Doctoral Thesis

On-line optimization and control of simulated moving bed processes

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On-line optimization and control of simulated moving bed processes

A dissertation submitted to the
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presented by

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Zurich 2004
Acknowledgement

I came to Zurich as a tourist and spent a day in the town in a gorgeous summer day. Leaving the town without visiting the ETH, one of the most famous universities in Europe, was not thinkable. I located the chemical engineering department and entered the building to see around. I should confess; I also knew that they had some exciting projects to work on. I saw the name of Prof. Morbidelli on the door and knocked the door. He was in his office. After four years, I am leaving the ETH with a PhD degree. What happened in between is partly in this thesis.

The ETH experience is indeed the most valuable one in my life up to date. It may be difficult to find a good PhD student but at least the pool of students has a significant volume; therefore, I believe it is more difficult to find a good boss. I had the chance to work with three excellent ones.

I would like to thank to Prof. Massimo Morbidelli first of all for being in the office in that particular day. It did not take too long to realize that finding him in his office was already a magic. I also would like to thank him for his humor and excellent support throughout my PhD studies.

Prof. Marco Mazzotti has been one of my three bosses throughout my PhD. He has been not only a perfect advisor but also a good friend. It has been a privilege to get to know him. His enthusiasm in my research was a significant motivation factor. Thanks for everything Marco. I had the chance to meet Prof. Hyun-Ku Rhee thanks to Marco. I also would like to thank him for his support and nice discussions.

I need to express my deepest gratitude for my advisor Prof. Manfred Morari. I had his full support at every single step of my PhD. I always had the confidence of having his backup. He has shown countless times that my personal development is as important as my scientific work for him. There has been difficult times; sometimes at work sometimes regarding my private life. He was always there for me not only as a supervisor but also as a friend to talk to.

I had the privilege to work with distinguished people. I would like to thank to the group of Prof. Morbidelli and Prof. Mazzotti. They accepted me as one of their members. Stefanie was my project partner for about three years and it was a pleasure to work with her. I believe that we carried out an excellent team work by sharing both the difficulties and the success. I appreciate her professional and personal skills. I also would like to thank to Aman. It was difficult to be the successor of Steffi, but it did not take too long to develop a personal connection with him. He has made a significant contribution to our project in a very short time.
Separating the work and the private life seems to be a trend. I always find it to be a sad one. I shared my life with my friends at IfA. I enjoyed spending time with them even after sharing a typical work day of 10-12 hours. I would like to thank to Saso, Giancarlo, Frank (master of Latex), Fabio, Mato, Valentina, Eleonora, Georgios and Marc. I had a great time with you guys. To Danielle, Martine, Esther and Alice (administrative staff of IfA), I would like to thank you for your support. Receiving a letter that I don’t understand was sometimes exhausting. You made everything easier for me. It was wonderful to have you taking care of everything. Thanks to Andrea and Gabi for being themselves and helping me and Özge anytime that we needed. My first officemate Francesco; my dear friend, you sing terrible but it is a privilege to be your friend. Thanks for your support! Pascal (my last officemate and a good cook) and Claudia; I believe that we developed a lifelong friendship. You are the parents of two of our kittens but this was only the beginning. We are considering you as the godfather and godmother of our future children. You better get prepared for more responsibility.

Being a wife of a PhD student is not easy. My wife Özge was always there for me and sharing with her was the best part of all. Nothing would have been tasty without her.

To the people in my homeland:

Kardeşim Özgürcan’a, Rezzan anneme, tüm Saç ve Çevik ailesine de destekleri için teşekkür ederim.

Anneme, babama ve ablama: Mutlu bir aile olduğumuz ve bana verdiginiz hersey için minnettarım. Her Türkiye’ye gidişimde beni en iyi lokantalara götürüp gözümü doyuran kardeşim Alp’i de unutmayım haliyle mümkün değil.
Abstract

In recent years Simulated Moving Bed (SMB) technology has become more and more attractive in the areas of pharmaceuticals, fine chemicals and biotechnology in which complex separation tasks are faced on daily bases. There are two striking advantages of SMB technology that make it a powerful alternative. Firstly, it delivers high productivity per unit mass of stationary phase with low solvent consumption compared to conventional chromatographic processes such as batch chromatography. Secondly, it allows a fast and reliable scale-up of separations from analytical chromatography, and therefore, a shorter time to market can be achieved.

Thorough understanding of the SMB process has led to optimization tools with different levels of complexity and to new SMB schemes, e.g., VARICOL [1], PowerFeed [2] and ModiCon [3], which allow for further improvements in the efficiency of the SMB units. Even though the possible gain from optimization of SMB processes is proven to be significant, the performance of the optimization algorithms is limited by the quality of the available physical data. Unfortunately it is also a fact that the precise characterization of the separation system is a rather difficult task. Moreover, the optimal conditions depend on the operating parameters, i.e., feed concentration/composition, and the physical parameters of the system, i.e., the adsorption isotherm and column properties, which are both subject to change. Therefore, frequent re-characterization of the system and re-optimization of the process are required to account for the changes. Another issue is the high sensitivity of the SMB units to the disturbances, e.g., pump or temperature instabilities, and to above uncertainties that may lead to sub-optimal operation conditions in the best case scenario and off-spec production in general. As a consequence, robust operation of the SMB plants at their economic optimum is still an open issue. The common practice is to operate the SMB units far from the optimal operating conditions to guarantee a certain level of robustness.

Development and implementation of robust SMB control schemes has the potential to deliver the full economic potential of the technology. On the other hand, feedback control of SMB process has been regarded as a challenging task for the standard control algorithms not only because of its periodic steady-state, nonlinear, mixed discrete and continuous nature but also due to long delays in exhibiting the effect of disturbances.

This thesis proposes a new on-line optimization based SMB control strategy, where a linearized time-varying reduced-order model, that accounts for the mixed discrete and continuous nature of the SMB process, is used to predict the evolution of the plant dynamics. Four internal flow rates, which can be adjusted via external flow rates, are
used as the manipulated variables. On-line concentration measurements at the product outlets together with a periodic Kalman filter are used to correct the possible model prediction errors. The SMB control problem is defined as a general constrained dynamic optimization problem to be solved on-line which yields the optimal control inputs allowing for the achievement of process specifications and optimal performance.

The developed SMB control scheme has several noteworthy features. Firstly, it only requires the knowledge of the adsorption behavior of the compounds under linear chromatographic conditions, even if the SMB unit operates under nonlinear chromatographic conditions. Hence, it makes the detailed adsorption isotherm measurements redundant. Secondly, it makes use of the average void fraction of the columns in the SMB loop, and therefore, it removes the necessity of detailed characterization of the columns. Hence, it addresses all the above difficulties.

The thesis demonstrates the effectiveness of the controller when applied to a virtual SMB plant in the case of systems characterized by both linear and nonlinear isotherms. The performance has been tested thoroughly under extreme model/plant mismatch conditions or large disturbances of various origins. Moreover, the proposed SMB control scheme has been experimentally validated by implementing on a lab-scale eight-column four-section SMB unit used for the high purity separation of the nucleosides (uridine and guanosine). The performance of the controller is proven via several test runs that are designed to challenge its robust performance. This is the first time that a standard experimental SMB plant, i.e., with four sections and two product outlets and used for high purity separation, is successfully optimized and controlled on-line.
Zusammenfassung

In den letzten Jahren wurden Simulated Moving Bed (SMB) Verfahren zu einer attraktiven Trennungsmethode in den Feldern Pharmaka und Feinchemikalien. Um jedoch das volle Potential der weitverbreiteten SMB Technologie auszuschöpfen, sind robuste Steuerungstechniken notwendig.


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Notation

$A, B, C$ discrete time state space matrices
$\tilde{A}, \tilde{B}, \tilde{C}, H, \tilde{\Psi}$ state space matrices of the time-to-time transition model
$A_c, B_c, C_c$ continuous time state space matrices
$A_{cr}$ column cross-section area, [cm$^2$]
$a_p$ specific surface of the adsorbent particles, [1/cm]
$c$ concentration, [g/L]
$c$ vector consists of the concentration values along the unit
$\tilde{c}$ dimensionless concentration variable
$c_{out}$ vector consists of the process outputs
$c^l$ solubility limit concentration, [g/L]
$D_{ap}$ apparent axial dispersion coefficient, [cm$^2$/s]
$\delta Q_{\text{max}}$ maximum allowable flow rate change
$\Delta U_{nc}$ vector of $n_c$-step future inputs
$f$ scalar-valued function
$f$ vector-valued function
$g$ scalar-valued function
$g$ vector-valued function
$h$ residual term in the model equations
$H_i$ Henry's constant of component $i$
$J_{fr}(c)|_{\text{ref}}$ Jacobian of $f^p$ with respect to $c$ evaluated at the reference profile
$J_{fr}(Q)|_{\text{ref}}$ Jacobian of $f^p$ with respect to $Q$ evaluated at the reference profile
$J_{g^c}(c)|_{\text{ref}}$ Jacobian of $g^p$ with respect to $c$ evaluated at the reference profile
$K$ Kalman filter gain matrix
$k$ cycle index
$k_i$ is the mass transfer coefficient of component $i$, [cm/s]
$L$ column length, [cm]
$m$ flow rate ratio
$N$ number of time steps per cycle
$n$ time index within a cycle
$n_c$ control horizon
$n_{col}$ number of columns constituting the SMB unit
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_{eq}$</td>
<td>number of ODEs constituting the SMB model</td>
</tr>
<tr>
<td>$\tilde{n}_{eq}$</td>
<td>number of states of the reduced-order lifted model</td>
</tr>
<tr>
<td>$n_g$</td>
<td>number of grid points defined along the column</td>
</tr>
<tr>
<td>$n_{col}^j$</td>
<td>number of columns in section $j$</td>
</tr>
<tr>
<td>$N_p$</td>
<td>number of theoretical plates</td>
</tr>
<tr>
<td>$n_p$</td>
<td>prediction horizon</td>
</tr>
<tr>
<td>$n_s$</td>
<td>number of species</td>
</tr>
<tr>
<td>$N_u$</td>
<td>number of inputs for the lifted cycle-to-cycle model</td>
</tr>
<tr>
<td>$n_u$</td>
<td>number of inputs</td>
</tr>
<tr>
<td>$N_y$</td>
<td>number of plant outputs for the lifted cycle-to-cycle model</td>
</tr>
<tr>
<td>$n_y$</td>
<td>number of plant outputs</td>
</tr>
<tr>
<td>$p$</td>
<td>index for different input/output configuration, i.e., $p = 1, \ldots, n_{col}$</td>
</tr>
<tr>
<td>$P$</td>
<td>covariance matrix of the estimate</td>
</tr>
<tr>
<td>$P_E$</td>
<td>purity of extract outlet</td>
</tr>
<tr>
<td>$P_R$</td>
<td>purity of raffinate outlet</td>
</tr>
<tr>
<td>$Q$</td>
<td>volumetric fluid flow rate, [mL/s]</td>
</tr>
<tr>
<td>$Q^*$</td>
<td>vector comprising internal flow rates</td>
</tr>
<tr>
<td>$q^*$</td>
<td>adsorbed phase concentration, [g/L]</td>
</tr>
<tr>
<td>$R_v$</td>
<td>covariance matrix of the noise sequence $v$</td>
</tr>
<tr>
<td>$R_w$</td>
<td>covariance matrix of the noise sequence $w$</td>
</tr>
<tr>
<td>$s$</td>
<td>slack variable</td>
</tr>
<tr>
<td>$S$</td>
<td>selectivity</td>
</tr>
<tr>
<td>$S_{\lambda_m}$</td>
<td>UV signal at wavelength $\lambda_m$, [AU]</td>
</tr>
<tr>
<td>$t$</td>
<td>time, [s]</td>
</tr>
<tr>
<td>$t^*$</td>
<td>switch time, [s]</td>
</tr>
<tr>
<td>$t_0$</td>
<td>retention time of non-retained species, [min]</td>
</tr>
<tr>
<td>$t_{R,i}$</td>
<td>retention time of component $i$, [min]</td>
</tr>
<tr>
<td>$u$</td>
<td>vector of manipulated variables, [mL/s]</td>
</tr>
<tr>
<td>$U$</td>
<td>vector grouping the input values for one cycle</td>
</tr>
<tr>
<td>$u_s$</td>
<td>superficial velocity, [cm/s]</td>
</tr>
<tr>
<td>$V$</td>
<td>volume of one column, [mL]</td>
</tr>
<tr>
<td>$v, w$</td>
<td>zero mean white noise sequences</td>
</tr>
<tr>
<td>$V_{d,j}$</td>
<td>dead volume per column in section $j$, [mL]</td>
</tr>
<tr>
<td>$V_{inj}$</td>
<td>injection volume, [$\mu$L]</td>
</tr>
<tr>
<td>$V_j$</td>
<td>volume of section $j$, [mL]</td>
</tr>
<tr>
<td>$w_i$</td>
<td>peak width at half height, [min]</td>
</tr>
<tr>
<td>$x$</td>
<td>state vector</td>
</tr>
<tr>
<td>$\tilde{x}$</td>
<td>state vector of the reduced order model</td>
</tr>
<tr>
<td>$y$</td>
<td>vector of output concentrations</td>
</tr>
<tr>
<td>$Y$</td>
<td>vector grouping the output values for one cycle</td>
</tr>
</tbody>
</table>
\( \mathcal{Y}^{low} \) vector of the output constraint trajectory over the prediction horizon

\( \mathcal{Y}^{mp} \) vector of \( n_p \)-step future outputs

\( z \) axial coordinate, [cm]

\( \tilde{z} \) state vector of the time-to-time transition model

\( \tilde{z}(n + 1|n) \) one-step-ahead prediction of the states based on the measurements at time \( n \)

**Greek letters**

\( \alpha \) pump calibration factors

\( \Delta \) backwards difference with respect to the cycle index \( k \)

\( \varepsilon \) bed void fraction

\( \Phi, \Gamma, \Pi, G \) state space matrices of the lifted model

\( \tilde{\Phi}, \tilde{\Gamma}, \tilde{\Pi}, \tilde{G} \) state space matrices of reduced-order lifted model

\( \eta \) dimensionless position variable

\( \lambda \) vector consists of the weighting factors

\( \lambda_n \) weighting factors in the cost function

\( \tau \) wavelength, [nm]

\( \tau_s \) sample points within a cycle

**Subscripts and superscripts**

\( ave \) average

\( D \) desorbent

\( E \) extract

\( F \) feed

\( g \) space index (grid point number)

\( G \) guanosine

\( h \) column position index, \( (h = 1, \ldots, n_{col}) \)

\( i \) component index, \( (i = A, B) \)

\( I/O \) inlet/outlet stream

\( in \) column inlet

\( j \) section index, \( (j = I..IV) \)

\( max \) maximum

\( meas \) measurement

\( min \) minimum

\( out \) column outlet

\( R \) raffinate
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDM</td>
<td>equilibrium dispersive model</td>
</tr>
<tr>
<td>HETP</td>
<td>height equivalent to a theoretical plate</td>
</tr>
<tr>
<td>LPV</td>
<td>Linear parameter varying</td>
</tr>
<tr>
<td>LTV</td>
<td>linear time varying</td>
</tr>
<tr>
<td>MPC</td>
<td>model predictive control</td>
</tr>
<tr>
<td>NN</td>
<td>neural network</td>
</tr>
<tr>
<td>ODEs</td>
<td>ordinary differential equations</td>
</tr>
<tr>
<td>PDEs</td>
<td>partial differential equations</td>
</tr>
<tr>
<td>RMPC</td>
<td>repetitive model predictive control</td>
</tr>
<tr>
<td>RSMB</td>
<td>reactive simulated moving bed</td>
</tr>
<tr>
<td>SMB</td>
<td>simulated moving bed</td>
</tr>
<tr>
<td>TMB</td>
<td>true moving bed</td>
</tr>
</tbody>
</table>
1

Introduction

The simulated moving bed (SMB) is a continuous multi-column chromatographic process that has become an attractive technology for complex and difficult separation tasks that are regularly encountered in the areas of pharmaceuticals, fine chemicals and biotechnology [4–7]. The underlying principle of the SMB is a countercurrent separation involving a liquid and a solid phase. The mixture to be separated enters at the feed-port and, in the case of a binary system, its two components move in opposite directions, i.e., one propagates in the direction of the solid and the other in the direction of the liquid stream, according to their affinity to either of the phases. The two purified components can be collected at the two outlet ports left and right of the feed-port. A process as described above involving a real countercurrent contact is called a True Moving Bed (TMB). Because it is difficult in practice to move the solid phase without damaging it or changing its properties, the TMB process has been regarded as infeasible. The SMB is a technical approximation of the TMB process that overcomes the problems connected to countercurrent continuous flow of the solid phase. It comprises a loop of several fixed-bed chromatographic columns where solvent is circulating in one direction. The continuous countercurrent solid flow is simulated by synchronous switches of the positions of the inlet and outlet streams one column position in the direction of the liquid flow. As a result, the SMB profits from the counter-current contact of the stationary and mobile phases without facing the difficulties connected with the movement of the solid phase. The detailed descriptions of the TMB and SMB processes are given in chapter 2.

The SMB technology attracts interest particularly in the area of chiral separations, e.g., for enantiopure drug development, where the resolution of enantiomers is usually a binary separation problem with low selectivities and high costs of solvent and chiral stationary phases. This is reflected by similar trends in the popularity of the SMB technology and the significance of the single enantiomer compounds in the global market. A survey by Frost & Sullivan shows that the revenues from chiral technologies will grow annually by at least 10% and reach $15 billion by the end of 2009 (see Table 1.1) [8]. Similarly, the single enantiomer drug sales will reach $172 billion and take up 48% of the global drug sales by 2005 [9].

Despite the growing business, pharmaceutical companies are generally working under the pressure of market competition. Therefore, they demand short development times to
expand their market share, and large-scale production methods with high productivity at low cost to increase their profit. These companies have different and conflicting interests for the early test and the further production phases. For instance, the ease and speed of the new separation designs are crucial for the early test stages, where they require only a few grams of the chiral drug for preliminary biological tests; therefore, the cost efficiency may not be an issue at all. On the other hand, reliability and cost efficiency of the applied techniques become the primary concern for the large scale productions. It is also important for them to use consistent techniques in different phases not to face difficulties concerning the regulations.

The reputation of the SMB technology is actually due to its ability to deliver the needs both for the early development and the further production stages mentioned above. Because the same stationary and mobile phase adopted for analytical purposes can be used, and because SMB units of different scales, i.e., from milligram per day to tons per day, are based on the same design principles, the SMB technology allows a fast and reliable scale-up of separations from analytical chromatography and offers a shorter time to market. For instance, it has been reported that the development of a new single enantiomer drug by SMB takes only months compared with two to five years for asymmetric methods, which in turn cost three to seven times more compared to SMB [8,10]. The survey by Frost & Sullivan estimates that, among the available technologies, chiral pool and separation currently contribute most to the revenues from chiral technologies, i.e., 55%. It also projects that the situation will not be much different in 2005 (see Figure 1.1) [8]. If we consider the 1200 metric tons per year installed SMB capacity in the pharmaceutical industry in 2003 [8], the remarkably increasing contribution of the SMB technology to the chiral business becomes evident.

The design of a new SMB separation requires the characterization of the adsorption behavior of the mixture to be separated and of the columns constituting the SMB unit. Once the physical data on the system are available, the existing modelling and optimization tools can be used to design and optimize the separation conditions [11–13].

<table>
<thead>
<tr>
<th>Year</th>
<th>Revenue [Billions]</th>
<th>Annual Growth [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>4.80</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>5.40</td>
<td>12.5</td>
</tr>
<tr>
<td>2001</td>
<td>6.10</td>
<td>13.0</td>
</tr>
<tr>
<td>2002</td>
<td>7.00</td>
<td>14.8</td>
</tr>
<tr>
<td>2003</td>
<td>7.74</td>
<td>10.6</td>
</tr>
<tr>
<td>2004</td>
<td>8.57</td>
<td>10.8</td>
</tr>
<tr>
<td>2005</td>
<td>9.53</td>
<td>11.1</td>
</tr>
<tr>
<td>2009</td>
<td>14.94</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Table 1.1: Revenues from chiral technology [8].
There are several issues that make this work difficult. First of all, it is difficult to characterize the system precisely, e.g., measurement of the competitive nonlinear isotherm parameters and of the single column packing properties. Obviously, the available design and optimization tools are limited by the accuracy of the available physical data. Moreover, in general, the system is subject to changes, e.g., chemical and mechanical aging of the stationary phase, so are the physical data. As a consequence, frequent re-characterization and re-optimization of the system are necessary. The second critical issue is related to the robustness of the SMB process. It has been shown that the higher the feed concentration or the feed throughput, the higher the sensitivity of the operation to perturbations and uncertainties, e.g., temperature deviations, pump inaccuracy, feed and solvent composition changes [11]. Hence, the operation of the SMB units close to their optimal operating conditions is difficult and not robust. For the reasons given above, SMB units are operated far from their optimal operating conditions in order to tolerate uncertainties in the system and minimize the effect of disturbances. In general, operating conditions of SMB units are controlled or tuned manually by experienced operators in order to keep the product specifications. Available short-cut design tools, such as Triangle Theory [11], provide explicit and simple rules and ease this task for the operators.

The focus of this thesis is the development and implementation of a control scheme that can overcome the above difficulties and make the SMB a more attractive tool over other technologies. Automatic control of SMB units has been regarded as a challenging problem for the standard control algorithms [14] because the SMB involves complex dynamics, e.g., its hybrid nature due to the inlet/outlet port switches, with nonlinearities and delays. Contrary to a significant number of works addressing its modelling, simula-
tion and optimization, there are only a few works on the control of SMB processes. The following section provides a short summary of the SMB control approaches available in the literature.

## 1.1 State of research on SMB control

The development of an SMB control concept has been challenging a number of research groups. These groups proposed model based control schemes that can be put into two main categories. The control strategies within the first category obtain the economic optimum of the process by off-line optimization techniques, i.e., based on detailed SMB models or short-cut methods such as triangle theory [11], by assuming that accurate physical data of the system is available a priori. The controllers are designed to operate the plant at the optimal operating conditions despite disturbances. They either make use of a TMB model to approximate the SMB dynamics or design their models such that the mixed continuous/discrete and non-steady-state nature of the SMB process is hidden from the controller. In this way, the difficulties connected with the hybrid nature of the process are overcome.

Kloppenburg and Gilles [14] proposed an automatic control scheme for an SMB unit applied to the separation of C₉ aromatics. The optimal operating conditions of the SMB unit are determined off-line from a TMB model. The same type of model is used to estimate and control the SMB behavior only at the middle of the switching intervals under the assumption that a TMB model represents the SMB dynamics well enough for systems with a high number of columns, e.g., 24 columns. The controller is designed using the principle of asymptotically exact input/output linearization.

Song and Rhee [15] obtained an input/output data-based prediction model by using subspace identification. Because the conventional linear identification methods can not be applied to a hybrid SMB process, they constructed a continuous input/output mapping by keeping the switch time constant and using a sampling interval equal to the switching period. The model inputs and outputs are defined as the flow rate ratios in the two central sections and the averaged concentrations of the target components in the plant outlets, respectively. The obtained model is then used to design a linear model predictive controller to keep the process on the pre-calculated optimal concentration trajectories despite the disturbances. They also addressed the performance of the controller for set point tracking.

Schramm *et al.* [16] introduced a concept that makes use of nonlinear wave propagation phenomena. Relationships between the front movements and the net flow rate ratios in every section of the equivalent TMB process are derived on the basis of the wave theory, which are then used to calculate the optimal operating conditions. The product purities are defined as the controlled variables and two PI controllers are used to adjust the movements of the wave fronts in the two central sections. The controller delivers the maximum feed throughput provided that the isotherm parameters are correct and the
regeneration of the solid and liquid phases is guaranteed.
The control strategies in the first group make use of rigorous SMB models or shortcut optimization tools in order to calculate the optimal operating trajectories and then define the control problem as a tracking or regulation problem. At the heart of them is the availability of accurate physical data of the system, which is the bottleneck for the optimal operation of SMB units itself. They also depend on the assumption that the optimal operating conditions of the SMB are known beforehand. However, it is hard to talk about optimal operating trajectories that are fixed a priori. Optimal profiles depend on the operating parameters, i.e., feed concentration and throughput, and the physical parameters of the system, i.e., adsorption isotherm, single column properties such as column void fraction and column efficiency, which are subject to change. Therefore, frequent re-characterization of the system and off-line re-optimization of the process are not avoidable.

The SMB control approaches within the second category tried to overcome these problems by introducing a two layer control scheme. On one level the process parameters, i.e., the physical properties characterizing the adsorption behavior of the species and the columns in the SMB loop, are estimated and/or the optimal operating trajectories of the process are calculated, i.e., corresponding to Controller 2 in Figure 1.2. On the other level the controllers are designed either to have the process follow the calculated optimal trajectories or to optimize the operating conditions on-line on the basis of estimated physical parameters, i.e., corresponding to Controller 1 in Figure 1.2.

Klatt et al. [17,18] introduced the first example of two layer control scheme. On the upper level the optimal operating trajectory of the process is calculated by off-line op-
timization, i.e., based on detailed SMB models. On the lower level, local SISO internal model controllers (IMC), i.e., based upon linear ARX type identification local models, are designed to keep the process on the optimal operating trajectory, i.e., to maintain the position of the internal profiles, despite the disturbances. They used a sampling interval equal to one switching period to avoid the difficulties introduced by the switching mechanism. Changes in the operating parameters necessitate estimation of the system parameters on the basis of on-line measurements, off-line re-optimization of the process to update the optimal trajectory, and re-synthesis of the local controllers based on the updated optimal trajectory on the upper level of the control architecture.

Because the control scheme with local linear models was found to be insufficient to maintain the position of the internal profiles under nonlinear chromatographic conditions, the same research group also investigated the neural network-based identification and model predictive control of SMB [19,20]. In that case, they identified multi-layer neural network (NN) models for the SMB process and obtained linear parameter varying (LPV) models by linearizing the identified NN models at each sampling instance. The LPV models are used within a standard linear MPC algorithm to keep the adsorption and desorption fronts at their pre-calculated optimal positions. This is done in order to avoid the difficulties of the nonlinear optimization problem within the nonlinear MPC strategy. Similar to the above control approaches, the switching time is regarded as the discrete sampling time of the system to hide the hybrid dynamics of the process from the controller.

Finally, Toumi and Engell [21] proposed a nonlinear MPC scheme that is applied to a three-section six-column reactive SMB (RSMB) unit (with 1-2-3 configuration). RSMB is used to combine the continuous chromatographic separation with the enzymatic biochemical conversion of glucose to fructose. Such an integration of reaction and separation is advantageous because the removal of reactants from the reaction zone overcomes the equilibrium limitations thus improving the process performance. Fructose is the only product; therefore, the considered RSMB scheme has only one product outlet. Actually, the proposed control scheme can be considered as the logical continuation of the ones presented previously by the same research group. In a sense that; they started with a relatively simple scheme based on local ARX type identification models [17,18], then took a further step in terms of computational complexity and used neural network models to represent the SMB dynamics. Linear parameter varying (LPV) models based on linearization of the identified NN models are employed to avoid the computational difficulties in nonlinear MPC [19,20]. Finally, in this scheme, they make use of a nonlinear rigorous process model for the on-line optimization of the process. Because the solution of a non-convex optimization problem may need formidable computational effort and time, they modified the control problem such that the emphasis is on the calculation of a suboptimal but feasible solution under real time constraints, i.e., the sampling time for the controller was defined as one switch period which was around 17 minutes for the considered SMB application. The authors state that “accurate values of the model parameters are needed for the use of the process model for optimization and
control". Therefore, necessary physical parameters are obtained beforehand by mathematical fitting of simulation runs to experimental data using the model parameters as optimization variables, and then adapted on-line with a similar algorithm by using available measurements. They report an experimental run with the proposed controller where they specify the desired product purity as 55%. The desorbent flow rate, recycle flow rate and switching period, i.e., modified only from cycle to cycle, were used as the manipulated variables. The task of the controller was to minimize the desorbent, i.e., water, consumption for a pre-defined feed flow rate. The controller managed to keep the product purity above the desired level. On the other hand, because of enzyme concentration changes from column to column, varying single column packing characteristics and temperature gradient over the columns, the product purity fluctuated above the specified level. The authors did not discuss the optimality of the operating conditions delivered by the controller, e.g., by comparing it to off-line optimization results for the given system with the estimated parameters or by means of other short-cut methods such as triangle theory applied to reactive SMB systems [22, 23]. Therefore it is hard to comment on the economic optimality of the operating conditions for the performed experimental run.

At the heart of all these control strategies is the availability and/or the on-line estimation of precise physical data of the system. The precise off-line characterization of the system is a challenging task in itself. Clearly, the on-line estimation of the system parameters is an even more difficult endeavor. Moreover, they depend on the perfection of the rigorous SMB models either for the off-line calculation of the optimal operating trajectories or for the on-line optimization of the process. Unfortunately, it is not easy to incorporate the effect of system uncertainties, e.g., uneven dead volumes in different sections of the SMB unit and the column-to-column packing differences that always exist in practice, on the optimal operating conditions or trajectories precisely. Finally, they define the periodicity of the process over successive switches. On the other hand, in reality, the process is periodic only cycle-to-cycle because of the above system uncertainties. As a consequence, the critical issue in SMB control is the robust performance of the control scheme under model and parameter uncertainties. Table 1.2 provides a summary of the SMB control schemes available in the literature.
<table>
<thead>
<tr>
<th>Approach</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controller 1</td>
<td>I/O Linearization</td>
<td>Linear MPC</td>
<td>PI</td>
<td>IMC based on local models</td>
<td>Linear MPC</td>
<td>Nonlinear MPC</td>
</tr>
<tr>
<td>Controller 2</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Optimization of operating conditions + Physical parameter estimation</td>
<td>Neural network adaptation</td>
<td>Physical parameter estimation</td>
</tr>
<tr>
<td>Controller 2 output</td>
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<td>None</td>
<td>None</td>
<td>Physical parameters + Optimal trajectory + Local models</td>
<td>Linear model parameters</td>
<td>Physical parameters</td>
</tr>
<tr>
<td>Controller 2 input</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Concentration + Flow rates</td>
<td>Concentration + Flow rates</td>
<td>Concentration + Flow rates</td>
</tr>
</tbody>
</table>

Table 1.2: Comparison of different SMB control approaches proposed by different research groups. I: Kloppenburg et al. [14], II: Song et al. [15], III: Schramm et al. [16], IV: Klatt et al. [17,18], V: Wang et al. [19,20], VI: Toumi et al. [21].
1.2 Contribution of this work

Model Predictive control (MPC) has proven to be a powerful control technique in the last two decades. The main advantage of MPC is its ability to handle multi-variable systems with time-delays and to explicitly cope with hard constraints both on the inputs and the states through on-line optimization [24, 25]. Recently, Lee et al. [26] formulated a new model predictive control (MPC) method, so-called repetitive model predictive control (RMPC), and proposed it for the control of periodic processes such as SMB chromatography [27]. RMPC makes use of the key concepts of repetitive control (RC) and combines them with the main ideas of model predictive control.

This thesis proposes an SMB control scheme that makes use of RMPC. The approach considers the control of the SMB units as a general constrained dynamic optimization problem and integrates the on-line optimization and control of the SMB process. It provides a general control strategy in which any type of economic objective can be used and all necessary product and/or process specifications can be considered explicitly as a part of the control algorithm. Most importantly, the developed control concept requires only minimal information on both the adsorption behavior of the mixture under consideration, i.e., only the knowledge of the linear adsorption isotherm, and the characteristics of the columns constituting the SMB unit, i.e., only the average void fraction of the columns in the SMB loop. This is a key improvement because SMBs are mostly operated under overloaded chromatographic conditions, i.e., corresponding to nonlinear competitive adsorption behavior, for which the determination of the nonlinear isotherm parameters constitutes the most demanding part of the system characterization and separation design. Especially in the case of enantiomer separations this may not be possible at all because a lack of pure enantiomers or the shortage of racemate is a common problem during the development stage of chiral drugs. On the other hand, contrary to nonlinear isotherm parameters, linear adsorption parameters, i.e., Henry's constants, are easy to access and their determination does not require pure components, e.g., the racemic mixture (1:1 mixture of the enantiomers) is sufficient in case of a chiral system. This thesis shows that the specified minimal information is sufficient for the on-line control and optimization of SMB processes regardless of the type of isotherm characterizing the adsorption behavior of the mixture to be separated. Thanks to these key features, the implementation of the control scheme removes the necessity of detailed characterization of the columns and of the adsorption behavior of the compounds. Hence, it addresses all difficulties mentioned above. To sum up the features of the developed control scheme:

- The control problem is formulated as a general constrained dynamic optimization problem and it gives the flexibility to choose the economic objective of the operation freely, e.g., minimization of the desorbent consumption, maximization of the productivity or combination thereof. Moreover, all product specifications and hardware limitations can be considered as constraints in the optimization problem.
- The control scheme does not require any a priori knowledge of optimal operating
The control scheme requires only a minimal number of physical parameter to be determined off-line once and for all.

- The knowledge of the adsorption behavior of the mixture under linear chromatographic conditions, i.e., characterized by linear adsorption isotherm parameters, and of the average void fraction of the columns in the SMB loop is sufficient even if the SMB unit operates under nonlinear chromatographic conditions. Hence, it significantly reduces the amount of necessary information for new SMB separations.

- It can handle the effects of extra-column dead volume differences among the sections and of column-to-column variations without any extra modelling effort.

Here the effectiveness of this control approach is demonstrated through extensive simulations in different cases, e.g., plant/model mismatch, various type of disturbances and uncertainties, both for systems characterized by linear and nonlinear adsorption isotherms. The efficiency of the control concept is proven by experimental studies using an eight-column four-section laboratory SMB unit. The performance of the control scheme is verified by addressing various situations that are similar to the ones considered in simulated studies. To my best knowledge, this thesis reports the first results on the on-line control and optimization of a standard experimental SMB unit, i.e., with four sections and two product outlets and used for a high purity separation. It also demonstrates the first and the only SMB control scheme that makes the information of linear adsorption isotherm sufficient for the on-line optimization based control of SMBs operating under nonlinear chromatographic conditions.

Note that presented work has been carried out as a collaboration of three institutes at ETH-Zurich, namely Automatic Control Laboratory (Prof. Manfred Morari), Institute of Process Engineering (Prof. Marco Mazzotti, Stefanie Abel and Mohammad Aman-Ullah) and Institute for Chemical and Bio-Engineering (Prof. Massimo Morbidelli). All the results in this thesis have been obtained as the outcome of this close collaboration. However, not all of the results which were obtained during my graduate studies are contained in this thesis. Please see Appendix B for a full list of publications.

1.3 Outline

The thesis is divided into six chapters. Chapter 2 comprises three sections. The first section discusses the evolution in the chromatographic processes and introduces the SMB process in detail. The second section provides the dynamic SMB modelling concept. The first-principle model of the process plays an important role in the development of the on-line optimization based model predictive control scheme. Moreover, it constitutes
the basis for a "Virtual SMB plant" that is used as a test platform for the developed SMB control scheme. Finally, the last section introduces the state-of-art shortcut design tool, i.e., so-called triangle theory, for SMB separations which provides simple algebraic equations that allow for the determination of the optimal and robust operating conditions of SMB units.

Chapter 3 is devoted to the on-line optimization based SMB control concept. It comprises four sections. The first section describes how to obtain a simplified explicit model of the process on the basis of the first-principle SMB models. The obtained model serves for on-line optimization and control purposes and constitutes the basis for the formulation of the control problem along the lines of RMPC. The second section discusses how to design a linear optimal state estimator that provides a recursive correction of the model errors. The third section introduces the model based prediction of the plant dynamics. The last section is dedicated to the optimization of the process performance and deals with the formulation of the optimization problem to be solved on-line.

Chapter 4 discusses the implementation of the developed control scheme on a virtual SMB plant. It has two sections. The first section addresses the control of SMBs operating under linear chromatographic conditions. The performance and the robustness of the control scheme are assessed for several simulated scenarios addressing the main challenges in the SMB operation. The second section addresses the control of SMB units operating under nonlinear chromatographic conditions. It demonstrates how the controller based only on the linear isotherm information can find the correct operating conditions for the separation of a system characterized by a competitive nonlinear Langmuir adsorption isotherm, and moreover, can optimize the economics of the operation. The performance of the control concept is evaluated under different scenarios that are commonly experienced by the SMB practitioners.

Chapter 5 is devoted to the implementation of the control concept on a laboratory eight-column four-section SMB plant arranged in a 2-2-2-2 configuration. The SMB is used for the high purity separation of the nucleosides, i.e., uridine and guanosine, retaining on the source 30RPC stationary phase according to a linear isotherm. The chapter has five sections. The first section introduces the experimental SMB setup. Section two is devoted to the characterization of the separation system. The third section describes the on-line measurement system used to continuously monitor the nucleosides concentration in the binary mixture of the product streams. The fourth section is devoted to the experimental verification of the SMB separation performance before implementing the control scheme. Moreover, it addresses the temperature sensitivity of the separation system in order to characterize the robustness of the SMB experiments. Finally the last section is devoted to the experimental test runs that are carried out to challenge the robustness of the controller and to prove its effectiveness.
Chapter 6 concludes the thesis and discusses possible future directions to be followed.
2

Background

2.1 Simulated moving bed chromatographic (SMB) process

Most of the chromatographic techniques were originally developed for analytical purposes but their separation power and ease of use have motivated chemical engineers to develop large-scale chromatographic production units. Chromatography has been regarded as the only general separation method in the pharmaceutical industry. Batch chromatography is one of the most studied and widely used separation techniques. The main drawbacks of this technology, i.e., low productivity and high operating cost, arise mainly from being a batch process. These drawbacks become more crucial at the full development and production stages as the cost becomes the major determining factor.

Continuous countercurrent chromatography, i.e., true moving bed (TMB), is an ideal process that overcomes the main drawbacks of batch chromatography. It has the ability to deliver high productivity per unit mass of stationary phase with low solvent consumption thanks to its continuous nature. It also provides the best possible mass transfer characteristics with the countercurrent contact of two phases which makes it an excellent choice for difficult separation tasks, e.g., systems with low selectivity. Continuous countercurrent chromatography can easily deliver two streams of products, e.g., two-component separation or separation of a multi-component feed into two parts, but design of the separation and product recovery become difficult if more than two product streams are of interest [28].

With reference to the scheme in Figure 2.1 and in case of a binary mixture, two inlet (feed, desorbent) and two outlet (raffinate, extract) streams divide the TMB units into four sections that operate with different liquid flow rates and have different functionalities. The feed stream enters the system continuously between two central sections, i.e., section II and III, where the separation is carried out. The less retained component B is carried upwards by the liquid phase and withdrawn at the raffinate outlet between section III and IV, while the more retained component A is adsorbed and carried downwards by the solid phase and collected at the extract outlet between section I and II. The light component B entering section IV is adsorbed in order to regenerate the liquid
Figure 2.1: Scheme of a true moving bed (TMB) unit.
2.1 Simulated moving bed chromatographic (SMB) process

Phase before being mixed with the fresh solvent and recycled to the section I. The section I is used to desorb the heavy component A and to regenerate the solid phase before it is recycled to the section IV.

In TMB chromatography, contrary to batch chromatography, overlapping of the fractions is not a concern as long as the solute concentration profiles are resolved enough to permit the collection of high purity products at the unit outlets. Therefore, the TMB units can be run under overloaded conditions resulting in high productivity and less diluted products which becomes critical at the recovery step of the solutes from the solvent. Unfortunately, TMB chromatography is one example that shows how a process with conceptual perfection may have a poor value in practice because TMB systems suffer from the difficulties in achieving proper continuous flow of the solid phase, the mechanical degradation due to significant shear forces, and low mass transfer efficiencies due to uneven packing properties.

Introduction of simulated moving bed (SMB) chromatography has been considered as a breakthrough in chromatographic applications because it can provide the benefits of countercurrent continuous operation without the problems associated with the continuous movement of the solid adsorbent. The key idea behind the SMB technology is the approximation of the continuous solid flow by moving the solid phase over a finite length at discrete times. SMB plants comprise a loop of several fixed-bed chromatographic columns (see Figure 2.2). The most widely adopted SMB configuration has a total of four inlet and outlet streams that divide the unit into four sections. Each of the sections consists of one or more fixed-bed columns. The continuous solid flow is simulated by successive synchronized movements of the two inlet (feed, desorbent) and two outlet (raffinate, extract) lines by one column position in the direction of the liquid flow. The corresponding solid phase velocity is defined as the ratio of the column length to the switch time. The higher the number of columns in each section, the closer the SMB unit to the corresponding TMB unit.

The operating principles of SMB units are similar to TMB units. Each section of the SMB plays a specific role in the process (see Figure 2.2). With reference to the separation of a binary mixture, the feed stream, carrying the mixture of more adsorbable component A and less adsorbable component B, is introduced between section II and III. The separation takes place in two central sections, where the less retained component B is eluted from section III before the port switching and collected at the raffinate outlet, whereas the more retained component A remains adsorbed in the solid phase until it is carried to the section I by the port switch, where it is eluted with fresh solvent and collected in the extract outlet. Component B is adsorbed in the section IV so that the eluent is regenerated before mixing with fresh eluent and recycled to the section I, where the adsorbent is regenerated by desorbing the component A. Note that the SMB process never reaches a steady-state with constant profiles of the process variables. The stationary regime of an SMB unit is a cyclic steady-state in which the process variables undergo a transient, e.g., the concentration profiles in the SMB propagate in the direction of the liquid and are shifted back at each port switch with respect to the
Figure 2.2: Scheme of a simulated moving bed (SMB) unit. Dash arrow indicates the inlet-outlet positions after the first switch.
Figure 2.3: Concentration profile of the less adsorbable component (B) and the more adsorbable component (A) in the SMB unit at different time instances within a switch period. Thick lines illustrate the profiles at the beginning of the switch, whereas the thin lines illustrate them close to the end of the switch period.
Figure 2.4: Concentration profile of the less adsorbable component (B) in the raffinate and the more adsorbable component (A) in the extract outlets of an SMB unit.
2.2 Modelling and simulation of SMB process

The conventional SMB units comprise four sections \((j=1, \ldots, IV)\) each of which has a volume of \(V_j = n_{col}^j V\), where \(n_{col}^j\) is the number of columns in section \(j\) and \(V\) is the volume of a column. For instance, Figure 2.2 illustrates a closed-loop four section SMB system arranged in a 2-2-2-2 configuration. The dynamics of each column constituting the SMB unit can be modelled in different level of complexity depending on the physical phenomena they include [34]. The equilibrium dispersive model (EDM) enforces the local equilibrium of the mobile and the stationary phases and lumps the effects of finite mass transfer rate and the axial dispersion in an apparent axial dispersion coefficient. Because it has been widely exploited for the design and optimization of chromatographic separations, and regarded as a good compromise between model accuracy and computational efficiency [29,35], EDM has been chosen to describe the single column dynamics in this work.

Let us define the following dimensionless concentration \(\tilde{c}_j\), time \(\tau\) and position \(\eta\)
variables

\[ \bar{c}_i = \frac{c_i}{c_i^l} \quad \tau = \frac{t}{t^*} \quad \eta = \frac{z}{L} \]  

(2.1)

where \( c_i^l, t^* \) and \( L \) are the solubility limit of component \( i \), the switch time, i.e., the period of time between two successive switches, and the length of the column, respectively. The equilibrium dispersive column model is as given below

\[ \epsilon_h \frac{\partial \bar{c}_i}{\partial t} + \frac{(1 - \epsilon_h)}{c_i^l} \frac{\partial q_i^*}{\partial t} + \frac{Q_h t^*}{A \epsilon_h L} \frac{\partial \bar{c}_i}{\partial \eta} = \frac{t^* \epsilon_h D_{ap,i}}{L^2} \frac{\partial^2 \bar{c}_i}{\partial \eta^2} \]  

(2.2)

In the above equation, \( D_{ap,i} \) is the apparent axial dispersion coefficient lumping the mass-transfer resistance and axial dispersion; \( Q_h \) and \( \epsilon_h \) are the volumetric flow rate and the total packing porosity in the \( h \)th column, respectively; \( q_i^* \) is the adsorbed phase concentration of component \( i \); \( A \) is the column cross-section area. The one-dimensional model accounts for different phenomena taking place in the column: accumulation in the fluid and solid phases via the first and the second terms and the convention via the last term on the left hand side; the term on the right hand side lumps the mass-transfer resistance and the axial dispersion in the fluid phase.

The adsorption isotherm model relates the concentration of component \( i \) in the solid phase to its concentration in the liquid phase

\[ q_i^* = f(c_i) \quad (i = A, B) \]  

(2.3)

A number of isotherm models for liquid-solid equilibrium are suggested and available in the literature [29, 36]. Any type of isotherm model, which suits best to describe the adsorption behavior of the mixture to be separated, can be incorporated into the EDM model. Only linear and nonlinear competitive Langmuir adsorption equilibrium isotherms are of main interest in this work.

**Linear isotherm:**

\[ q_i^* = H_i c_i \quad (i = A, B) \]  

(2.4)

where \( H_i \) is the Henry's constant of component \( i \).

**Non-linear isotherm:** Competitive Langmuir isotherm

\[ q_i^* = \frac{H_i c_i}{1 + K_i c_i + K_B c_B} \quad (i = A, B) \]  

(2.5)

where \( K_i \) is the equilibrium constant of the \( i \)-th component. Note that the linear isotherm can be considered as a special case of Langmuir isotherm because the Langmuir isotherm converges to linear isotherm (eq 2.4) when the concentration of species in the liquid phase is very small, i.e., \( c_i^l = c_i^A + c_i^B \) approaches zero.
The dynamic model of the SMB process is obtained by interconnecting the dynamic models of the single chromatographic columns. The boundary and initial conditions together with the material balances at the inlet/outlet nodes, i.e., connecting the single column models one to the other, complete the mathematical model of the SMB unit. The inlet/outlet switching mechanism of the process is considered explicitly by changing the node balance equations as described below.

Initial conditions:

In this work, it is assumed that the columns constituting the SMB unit are initially saturated with mobile phase in equilibrium with the stationary phase and the concentrations of both components are zero along all the columns

\[ \bar{c}_{i,h} = 0 \quad \forall \eta, \tau = 0 \quad \text{for} \quad h = 1, \ldots, n_{\text{col}} \tag{2.6} \]

where \( n_{\text{col}} \) is the number of chromatographic columns constituting the SMB unit.

Boundary conditions:

\[ \bar{c}_{i,h}^{\text{in}} = \bar{c}_{i,h} |_{\eta=0}^{+} \quad \forall \tau \quad \text{for} \quad h = 1, \ldots, n_{\text{col}} \tag{2.7} \]

\[ \frac{\partial \bar{c}_{i,h}}{\partial \eta} |_{\eta=1} = 0 \quad \forall \tau \quad \text{for} \quad h = 1, \ldots, n_{\text{col}} \tag{2.8} \]

where \( \bar{c}_{i,h}^{\text{in}} \) is the concentration of component \( i \) fed into the column \( h \) [29].

Node Balances:

Let us consider an SMB unit comprising eight fixed bed chromatographic columns, i.e., \( n_{\text{col}} = 8 \) and \( h = 1, \ldots, 8 \).

\[ Q_1 = Q_8 + Q_{1,1}^{I/O} \tag{2.9} \]

\[ Q_1 \bar{c}_{i,1}^{\text{in}} = Q_8 \bar{c}_{i,8}^{\text{in}} + Q_{1,1}^{I/O} \bar{c}_{i,1}^{I/O} \tag{2.10} \]

\[ Q_{h+1} = Q_h + Q_{h+1}^{I/O} \quad \text{for} \quad h = 1, \ldots, 7 \tag{2.11} \]

\[ Q_{h+1} \bar{c}_{i,h+1}^{\text{in}} = Q_h \bar{c}_{i,h}^{\text{in}} + Q_{h+1}^{I/O} \bar{c}_{i,h+1}^{I/O} \quad \text{for} \quad h = 1, \ldots, 7 \tag{2.12} \]

where \( \bar{c}_{i,h}^{\text{out}} \) is the concentration at the outlet of component \( i \) at column \( h \). \( Q_{h}^{I/O} \) identifies the flow rate of the inlet or the outlet stream entering or leaving the SMB loop just before column \( h \) and \( \bar{c}_{i,h}^{I/O} \) is the concentration of component \( i \) in the corresponding stream. In the equations above \( Q_h \) stands for the volumetric flow rate in column \( h \), which is the same for the columns belonging to the same section, e.g., \( Q_1 = Q_2 = Q_1, Q_3 = Q_4 = Q_{III}, Q_5 = Q_6 = Q_{III}, Q_7 = Q_8 = Q_{IV} \) for the SMB configuration given
Table 2.1: Flow rates of the inlet/outlet streams entering/leaving the SMB loop and the concentration of component \( i \) in the corresponding stream at successive switch periods.

- The system of partial differential equations (PDEs) of the SMB model can be reduced to a system of ordinary differential equations (ODEs) by finite-difference approximation of the first-order spatial derivatives. It is common practice to replace the apparent dispersion term by numerical dispersion to obtain a computationally efficient solution of the EDM [35]. The SMB process can be simulated efficiently, i.e., faster than in real time, by integrating the system of ODEs in time by a commercial stiff integrator. Note that a different set of ODEs is applicable for each port configuration of the SMB unit because input/output switching mechanism is explicitly imposed on the node balances.

- The nonlinear dynamic model of the SMB is used to simulate the process. The simulation platforms are developed both in Fortran language and in MATLAB environment. Because simulations can be performed much faster by using Fortran language, the simulation platform in Fortran language is used by interacting with MATLAB via Fortran MEX-files [37]. For the sake of clarity, the simulated process is referred to as "SMB plant" whenever used as a virtual test platform for the controller, namely in chapter 4.
2.3 Triangle theory: a shortcut design tool for SMB separations

Modelling of SMB units has been widely studied by several research groups and models with different complexity are available for the design and optimization of SMB separations [35,38,39]. An important contribution was made by the introduction of a short-cut separation design method, the so-called triangle theory [11]. The triangle theory introduced several advantages for the design and operation of SMB units. It allows to choose near-optimal and robust operating conditions based on a few algebraic computations for several type of adsorption equilibrium isotherms of greatest practical interest, e.g., linear, nonlinear competitive Langmuir and Bi-Langmuir adsorption isotherms. Moreover, it provides a thorough understanding of how the feed composition and the flow rate changes affect the separation performance. Hence, it has been widely exploited by the SMB practitioners. For the sake of completeness, a short summary of the Triangle theory results focusing on the systems characterized by linear and nonlinear Langmuir isotherms are provided here; a detailed description of the theory and its experimental verification can be found elsewhere [11,40-42].

The triangle theory defines the key operating parameters as the ratio of the net fluid and solid phase flow rates in each section of the SMB unit

\[ \frac{Q_j t^* - V e}{V(1 - e)} \]  

and derives the separation conditions on the basis of the equilibrium theory model, i.e., on the assumption that the axial mixing and the mass transfer resistance are negligible and the adsorption equilibrium is established everywhere in the columns instantaneously.

The necessary and sufficient conditions on the operating parameters for the complete separation of a system characterized by a linear adsorption isotherm (eq 2.4) are given by the following inequalities

\[ H_A < m_I < \infty \]  
\[ H_B < m_{II} < m_{III} < H_A \]  
\[ 0 < m_{IV} < H_B \]

under the assumption that nonporous particles constitute the solid phase. If the flow rate ratios in section I and IV fulfill the necessary conditions (eq 2.14 and eq 2.16), the operating parameters \( m_{II} \) and \( m_{III} \) define a plane which is divided into several regions characterizing the separation performance (Figure 2.5). First of all, the separation can take place if and only if \( m_{II} < H_A \) and \( m_{III} > H_B \) because violation of the former or the latter constraint leads to flooding of the extract or raffinate outlet with the solvent, respectively. The triangular area defined by the inequality (2.15) is the region where both the raffinate and extract outlets are pure. Note that \( m_{II} < m_{III} \) in the
Figure 2.5: The \((m_{III}, m_{III})\) operating parameter space for a system characterized by a linear adsorption isotherm.

Figure 2.6: The \((m_{IV}, m_{I})\) operating parameter space for a system characterized by a linear adsorption isotherm.
same inequality implies a positive feed flow rate. For the operating points constituting
the region defined by \( m_{II} < H_B \) and \( H_B < m_{III} < H_A \), the less retained component
\( B \) is carried to the extract outlet and the purity for the extract is low, whereas the
purity of raffinate is not affected. On the other hand, the region where \( m_{III} > H_A \)
and \( H_B < m_{II} < H_A \) defines the operating points where the raffinate outlet is polluted
and the extract purity is not affected. All the product streams have poor purity for the
operating points corresponding to the region \( m_{III} > H_A \) and \( m_{II} < H_B \).

As mentioned above, the separation performance is characterized by the position of
the operating point on the \((m_{II}, m_{III})\) plane, as well as on the \((m_{IV}, m_I)\) plane (Figure
2.6). The violation of the constraint on the operating variable \( m_I \), i.e., \( H_A > m_I \), leads
to incomplete regeneration of the solid phase and results in poor raffinate purity. On the
other hand, violation of the constraint on the operating variable \( m_{IV} \), i.e., \( m_{IV} > H_B \),
leads to pollution of the extract stream due to incomplete regeneration of the mobile
phase.

In general, the performance of the SMB separation is optimized either by aiming to
minimize the amount of stationary phase that is used to separate a given amount of
feed or to maximize the amount of feed that is separated in a given SMB unit with a
fixed amount of stationary phase. Therefore, the productivity (PR), i.e., mass of pure
product recovered per unit time and unit mass of stationary phase, is one of the key
performance parameters to be maximized in the SMB operation

\[
PR = \frac{\text{amount separated per time}}{\text{mass of stationary phase}} = \frac{Q^F c_F^E}{n_{col} V \rho_s (1 - \varepsilon)} = \frac{(m_{III} - m_{II}) c_F^E}{n_{col} t^* \rho_s}
\] (2.17)

where \( \rho_s \) is the solid bulk density. Another key performance parameter is the desorbent
requirement (DR) that is defined as the mass of desorbent used to recover a unit mass
of pure product

\[
DR = \frac{\text{desorbent consumption}}{\text{amount separated}} = \frac{(Q^D + Q^F) \rho_D}{Q^F c_F^E} = \frac{\rho_D}{c_F^E} \left( 1 + \frac{m_I - m_{IV}}{m_{III} - m_{II}} \right)
\] (2.18)

where \( \rho_D \) is the solvent density. Note that the density of the feed stream is assumed to
be equal to the solvent density because of its high dilution. It is obvious from eq 2.17 and
eq 2.18 that, for a constant switching time \( t^* \) and total feed concentration \( c_F^E \), both
performance parameters, i.e., productivity (PR) and desorbent requirement (DR), improve
by increasing the difference \( (m_{III} - m_{II}) \), i.e., by moving from the diagonal towards the
vertex of the triangular complete separation region in Figure 2.5. As a consequence, the
vertex of the complete separation region \( W_1 \) represents the optimal operating conditions
in terms of solvent consumption and productivity per unit mass of stationary phase (see
Figure 2.5). Similarly, the minimum possible solvent consumption corresponds to the
vertex of the rectangular complete regeneration area, i.e., the operating point indicated
as \( W_2 \) in Figure 2.6.

Concerning the separation of a mixture characterized by a nonlinear competitive Lang-
muir adsorption isotherm (eq 2.5), the necessary and sufficient conditions for complete
separation are as follows

\[ H_A = m_{I,\text{min}} < m_I < \infty \]  
\[ m_{II,\text{min}} < m_{II} < m_{III,\text{max}} \]  
\[ 0 < m_{IV} < m_{IV,\text{max}} \]

where,

\[ m_{II,\text{min}} = f(m_{III}, H_i, K_i, c_i^F) \]  
\[ (i = A, B) \]  
\[ m_{III,\text{max}} = f(m_{II}, H_i, K_i, c_i^F) \]  
\[ (i = A, B) \]  
\[ m_{IV,\text{max}} = \frac{1}{2} \left\{ H_B + m_{III} + K_B c_B(m_{III} - m_{II}) \right\} \]

\[ - \sqrt{\left[H_B + m_{III} + K_B c_B(m_{III} - m_{II})\right]^2 - 4H_B m_{III}} \]  

The first and last constraints (eq 2.19 and eq 2.21) guarantee the complete regeneration of the stationary and liquid phases in section I and IV, respectively, whereas the constraints on the operating parameters \( m_{II} \) and \( m_{III} \) guarantee the complete separation of the components in the two central sections. Note that the operating parameters \( m_I \) and \( m_{IV} \) have explicit lower and upper bounds and the constraints on \( m_I \) does not depend on the other flow rate ratios (see eq 2.19 and eq 2.21). On the other hand, the upper limit for \( m_{IV} \) is an explicit function of the flow rate ratios \( m_{II} \) and \( m_{III} \) (eq 2.24). The constraints on \( m_{II} \) and \( m_{III} \) (eq 2.20) do not depend on the flow rate ratios \( m_I \) and \( m_{IV} \); hence they define an operating region on the \((m_{II}, m_{III})\) plane as in the case of the linear isotherm (see Figure 2.7). On the other hand, contrary to linear adsorption isotherm, in case of a separation system characterized by nonlinear Langmuir isotherm, the boundaries of the complete separation region become functions of not only the adsorption isotherm parameters, but also the feed composition (see eq 2.22 and eq 2.23). Figure 2.8 illustrates the effect of the total feed concentration on the complete separation region. Note that the nonlinear Langmuir isotherm (eq 2.5) approaches the linear isotherm (eq 2.4) at very low fluid phase concentrations. As a consequence, the operating constraints on the flow rate ratios \( m_j \) for the Langmuir isotherm (eqs 2.19 to 2.21) approach those for the linear adsorption isotherm (eqs 2.14 to 2.16) at low concentrations, i.e., \( c_F^F = c_A^F + c_B^F \) approaches zero. Finally, according to the triangle theory, the optimum operating conditions in terms of productivity per unit mass of stationary phase and solvent consumption correspond to the vertex of the complete separation region, i.e., indicated as \( W_3 \) in Figure 2.7, as in the case of a separation system characterized by linear adsorption isotherm.
2.3 Triangle theory: a shortcut design tool for SMB separations

Figure 2.7: The \((m_{III}, m_{III})\) operating space for a system characterized by a nonlinear adsorption isotherm.

Figure 2.8: The effect of the total feed concentration on the \((m_{III}, m_{III})\) operating space.
3

Development of on-line optimization based control concept for SMB processes

It has been shown that the possible gain from optimization of SMB processes is significant \([11-13]\). On the other hand, regardless of their complexity, the performance of optimization algorithms is limited by the quality of the available physical data. Unfortunately, it is also a fact that the precise measurement of multicomponent adsorption isotherms, i.e., the key physicochemical properties characterizing the separation, is rather difficult task. Another issue is the significant dependency of the optimal conditions on the operating parameters, i.e., feed concentration/composition, and the physical parameters of the system, i.e., the adsorption isotherm and column properties, which are both subject to change. Therefore, it is hard to discuss a set of a priori fixed optimal operating conditions for SMB units. Re-characterization of the system and re-optimization of the process are required to account for the changes. As a consequence, the automatic control of SMB units presents itself as a dynamic optimization problem rather than a simple regulation or tracking problem, and integration of feedback control and on-line optimization is desirable to exploit the full economic potential of the SMB technology.

This thesis proposes a control strategy that is based on on-line dynamic optimization of the SMB process. The control scheme makes use of an explicit SMB model to predict the future evolution of the plant on the basis of its current state and to optimize its operating performance based on the desired economic objective (see Figure 3.1 for the scheme of the control concept). The internal flow rates in four sections, i.e., \(Q_j\), where \(j = I, \ldots, IV\), are used as the manipulated variables. Note that the key variables that characterize the SMB performance in the framework of triangle theory are the flow rate ratios in the four sections, i.e., \(m_j\) values, and they are linear functions of the internal flow rates \(Q_j\) (see eq 2.13). The RMPC formulation requires a defined period; therefore, the cycle time, i.e., \(n_{col} \times t^*\) where \(n_{col}\) is the number of columns in the SMB loop, is defined at the beginning of the operation, and the switching time \(t^*\) is not employed as a manipulated variable. Note that it is hard to access the internal flow rates directly; therefore, it is common practice to manipulate them by acting on one internal and three external flow rates, e.g., \(Q_I, Q^E, Q^R\) and \(Q^F\).
The concentration levels in the two outlet streams, i.e., extract and raffinate, constitute the measured variables, i.e., \( c^R_A, c^R_B, c^E_A \) and \( c^E_B \). Therefore, the control scheme requires two on-line measurement systems installed at the raffinate and extract outlets in order to monitor the concentration of each component. For chiral separations, the state of the art on-line measurement system is based on the coupling of a UV detector and a polarimeter at each outlet of the SMB unit. The UV detector provides the absorbance of the mixture that is proportional to the sum of the outlet concentrations, i.e., \( c^R_A + c^R_B \) and \( c^E_A + c^E_B \), whereas the polarimeter provides a signal that is proportional to the concentration difference, i.e., \( c^R_A - c^R_B \) and \( c^E_A - c^E_B \). Two independent signals coming from the UV and the polarimeter can be used to calculate the absolute enantiomer concentration at the outlets [43]. For non-chiral separations, the difference in the UV spectra of the species can be exploited in order to monitor their on-line concentrations. In this case, one multi-wavelength UV detector for each outlet stream is sufficient. The absorbance of the mixture can be measured at two different wave-lengths simultaneously, and the corresponding independent signals can be used in order to calculate the absolute concentration of the species at the product outlets.

The control problem is defined such that the performance of the plant is optimized over a predefined future time window, i.e., *prediction horizon* \((n_p)\). The objective function of the optimization problem is defined along the lines of the main interest in the operation, e.g., maximum productivity and/or minimum desorbent consumption. The product specifications, i.e., outlet purities, as well as the hardware limitations, e.g., maximum...
allowable pressure drop in the columns, are considered explicitly as the constraints of the optimization problem. The on-line solution of the optimization problem yields the optimal changes in the manipulated variables, i.e., the flow rate changes resulting in the optimal performance, for a chosen future time window, i.e., control horizon \( (n_c) \). The optimal flow rate sequence is implemented according to a receding horizon strategy. Hence, the first element of the calculated optimal flow rate sequence corresponding to the current time \( t \) is implemented on the plant and the remaining elements are discarded. A new optimization problem is solved at time \( t + 1 \) based on the information coming from the new measurements collected from the plant.

The underlying idea of RMPC is that possible model prediction errors and the effect of periodwise constant disturbances are likely to repeat from cycle to cycle and can be estimated by using the available measurements of the plant output, which is then used to correct for the possible model prediction errors in the future cycles. A periodic Kalman filter is used to combine the measurement information and the model estimation in an optimal sense to correct the model errors recursively [44].

### 3.1 Modelling

How to obtain a model of the SMB process for control purposes has been one of the main challenging issues for the research groups working on the SMB control problem. On one hand, an SMB model that represents the key characteristics of the process, i.e., its hybrid (continuous/discrete) and periodic dynamics, is desirable. On the other hand, there is a clear need for a trade-off between the complexity of the model and the burden of computation that it introduces.

One extreme is the usage of detailed nonlinear dynamic SMB models, such as described in section 2.2, in the available control algorithms such as nonlinear model predictive control strategies. However, on-line optimization of the process on the basis of detailed dynamic SMB models, which lead to nonlinear programming problems, is difficult because of the needed modelling effort and the excessive computation time requirement. Therefore, in general, the nonlinear model predictive control problems are modified such that the emphasis is put on the calculation of a suboptimal but feasible solution under real-time constraints [21].

Most of the research groups followed the other extreme and tried to overcome the problem by obtaining black-box models with the available model identification techniques [15,17-20]. These models are designed such that the discontinuities introduced by the switching operation and the periodic nature of the process are hidden for instance by using a sampling interval equal to the switching period.

This section addresses the above problem and introduces a methodology to obtain a simplified SMB model on the basis of first-principle models.
3.1.1 Simplification of the dynamic SMB model for control purposes

In this thesis a linear time-varying (LTV) SMB model based on the dynamic modelling concept described in section 2.2 is employed. The developed LTV SMB model captures both the hybrid and periodic nature of the process explicitly. In the following, a step-by-step description of the modelling procedure, i.e., starting from the detailed SMB model based on EDM and ending up with the LTV SMB model, is given.

The dynamic modelling of the SMB process based on EDM leads to a description with partial differential equations. The model comprises one PDE for each species and column. For instance, in case of an eight-column SMB unit and with reference to a binary mixture, the PDE system comprises 16 partial differential equations (PDEs) in the following form (see section 2.2 for details).

\[ \frac{\partial c_{j,h}}{\partial \tau} + \frac{(1 - \varepsilon_h)}{c_l^i} \frac{\partial q_{i,h}}{\partial \tau} + \frac{Q_h t^*}{A_{Ne} L} \frac{\partial \varepsilon_{k,h}}{\partial \eta} = \frac{t^* \varepsilon_h D_{ap,i} \partial^2 \varepsilon_{k,h}}{L^2} \]

The resultant equation system requires information about the system under consideration, e.g., adsorption isotherm, total packing porosity of each column ($\varepsilon_h$), and the effect of the apparent axial dispersion ($D_{ap,i}$), in order to describe the system dynamics. Obviously, it is desirable to have a control strategy that is based on the least possible information on the system. Hence, the trade-off between the required information and the achievable control quality is one of the key issues in the SMB control problem.

**Adsorption isotherm:** The information about the competitive adsorption isotherm is not easily accessible due to reasons mentioned above, whereas the linear adsorption isotherm parameters, i.e., Henry's constants, can be determined easily and precisely by measuring the retention time of a pulse of each species at very low fluid phase concentrations corresponding to linear chromatographic conditions, i.e., $c_F^i = c_A^i + c_B^i$ approaches zero. Besides, their determination does not require pure enantiomers but only the race-mate, i.e., 1:1 mixture of the enantiomers, because there is no competition between the species under linear chromatographic conditions. Hence, it would be a major advantage to use an SMB model that is based only on the knowledge of the linear adsorption isotherm. Even though the dynamics of SMBs operating under linear and nonlinear chromatographic conditions differ in many ways, e.g., the propagation of internal concentration profiles in the columns, the underlying dynamics and operating principles are very similar, e.g., the functionalities of the sectional flow rates and their influences on the product purities. In this work, the information of linear adsorption isotherm is found to be sufficient for on-line optimization and control purposes regardless of the isotherm type characterizing the adsorption behavior of the separation mixture. Therefore, the SMB model used in the control scheme is obtained by incorporating the below linear isotherm model into the EDM (eq 3.1).

\[ q_{i,h}^* = H_i \varepsilon_{i,h} \quad (i = A, B) \]
Total packing porosity ($\varepsilon_h$): It is not possible to pack all columns in exactly the same way; therefore, column-to-column differences are not avoidable in practice. It is possible to determine the overall void fraction of each column by measuring the retention time of a non-retained species. On the other hand, during the design of an SMB separation, it is common practice to assume that the chromatographic columns constituting the SMB unit have identical packing characteristics. The same assumption will be exploited here by assigning an average packing porosity to all columns in the SMB loop, i.e., $\varepsilon_h = \varepsilon_{ave}$ for $h = 1 \ldots n_{col}$.

Apparent axial dispersion ($D_{ap,i}$): The EDM accounts for the effect of mass transfer resistance and the axial dispersion by introducing an apparent axial dispersion coefficient, i.e., $D_{ap,i}$, as described in section 2.2. On the other hand, replacement of the apparent axial dispersion term by numerical dispersion (with the assumption that the dispersion for all components is identical) is a widely used technique to obtain a computationally efficient solution of the equilibrium dispersive model [34]. Hence, this approach will also be exploited here as a simplification technique.

Let us follow the standard practice and define $n_g$ grid points along each column constituting the SMB unit in order to approximate the spatial derivatives by finite differences and reduce the PDE system of SMB into a system of ODEs. Backwards approximation of the first-order spatial derivative in the equilibrium dispersive model (eq 3.1) and incorporation of the linear adsorption isotherm (eq 3.2) result in

$$\frac{\partial \tilde{c}_{i,h,g}}{\partial t} + \frac{Q_{h,t^*}}{A_{cr} (\varepsilon_h + (1 - \varepsilon_h) H_i) L} \left( \frac{\tilde{c}_{i,h,g} - \tilde{c}_{i,h,g-1}}{\Delta \eta} + \frac{\partial^2 \tilde{c}_{i,h,g}}{\partial \eta^2} \frac{\Delta \eta}{2} + O(\Delta \eta^2) \right) = \frac{t^* \varepsilon_h D_{ap,i}}{(\varepsilon_h + (1 - \varepsilon_h) H_i) L^2} \frac{\partial^2 \tilde{c}_{i,h,g}}{\partial \eta^2}$$

(3.3)

where $g$ is the space index, i.e., $g = 1 \ldots n_g$, and $\Delta \eta$ is the space interval.

$$\Delta \eta = \frac{1}{n_g}$$

(3.4)

The neglected terms in the approximation are proportional to $\Delta \eta^2$. Note that under the assumption of identical axial dispersion for all components, i.e., $D_{ap,i} = D_{ap}$, if the space interval $\Delta \eta$ is chosen such that

$$\Delta \eta = \frac{2 \varepsilon_h D_{ap}}{Q_h L}$$

(3.5)

then the numerical error due to approximation of the first spatial derivative becomes equal to the apparent axial dispersion term on the right hand side of eq 3.3.
As a result, the effect of a constant apparent dispersion term can be accounted for by means of numerical dispersion which reduces the equilibrium dispersion model (eq 3.3) into the “ideal model” of chromatography.

\[
\frac{\partial \hat{c}_{i,h,g}}{\partial \tau} + \frac{Q_{h,t}}{A_{cr} (\frac{1}{1 - \epsilon_h}) H_i } \left( \frac{\hat{c}_{i,h,g} - \hat{c}_{i,h,g-1}}{\Delta \eta} \right) = 0 \tag{3.7}
\]

In case of the equilibrium dispersive model (eq 3.3) and infinite dilution linear conditions (eq 3.2), the number of theoretical plates is given by the following relationship [29].

\[
N_{p,i} = \frac{Q_h L}{2 \epsilon_h D_{ap,i} A_{cr}} \tag{3.8}
\]

It can be observed from eq 3.4, eq 3.5 and eq 3.8 that the number of theoretical plates is equal to the number of grid points defined along the column.

\[
N_{p,i} = \frac{1}{\Delta \eta} = n_g \tag{3.9}
\]

Because the operating conditions, i.e., flow rates, in the four sections of the SMB unit are different, the column efficiency in each section may actually vary (see eq 3.8). On the other hand, one can see from eq 3.9 that identical space discretization for all the columns corresponds to the assumption that the columns belonging to the different sections have the same efficiency.

Concerning the SMB units operating under nonlinear chromatographic conditions, the equivalence of numerical dispersion and apparent axial dispersion term, i.e., the equivalence of the ideal model (eq 3.7) and the equilibrium dispersive model (eq 3.3), is only an approximation because SMB units operating at overloaded conditions require nonlinear isotherms to describe the phase equilibrium, and the apparent dispersion coefficient, contrary to linear chromatography, is concentration dependent for nonlinear chromatography. On the other hand, it has been shown that this approximation leads to satisfactory results also in nonlinear chromatographic applications even with a small number of stages, i.e., \(N_{p,i} < 100\), [29,34,35,45,46].

Note that for a given plant layout, i.e., total number of columns constituting the SMB unit, their dimensions and distribution to the sections, the ideal model (eq 3.7) requires only the Henry's constants, i.e., \(H_i\) for \(i = A, B\), and the total packing porosity that is assumed to be constant for all the columns, i.e., \(\epsilon_h = \epsilon_{ave}\) for \(h = 1 \ldots n_{col}\). As a consequence, the ideal model of chromatography poses itself as a convenient model not only because of its simplicity, but also because of its satisfactory ability to describe the most important features of the process.

Note that two ODEs (eq 3.7) per grid point, i.e., one for each species \((i = A, B)\), are required to define the space composition profiles as a function of time. For instance, with reference to the separation of a mixture of \(n_s\) species and an SMB unit that comprises \(n_{col}\) columns, the ODE set has

\[
n_{eq} = n_s \times n_g \times n_{col} \tag{3.10}
\]
equations describing the internal profiles of the species as a function of time and position along the SMB unit. Incorporation of the following initial and boundary conditions together with the node balances, i.e., given in eqs (2.9) to (2.12), into the system of ordinary differential equations complete the mathematical model of SMB.

**Initial conditions:** Following from eq 2.6:

\[ \bar{c}_{i,h,g} = 0 \quad \text{for} \quad \tau = 0, \quad g = 1, \ldots, n_g \quad \text{and} \quad h = 1, \ldots, n_{col} \]  

(3.11)

**Boundary conditions:** Following from eq 2.7 and eq 2.8:

\[ \bar{c}_{i,h,0} = \bar{e}_{i,h}^{in} \quad \forall \tau \quad \text{for} \quad h = 1, \ldots, n_{col} \]  

(3.12)

\[ \bar{c}_{i,h}^{out} = \bar{c}_{i,h}^{eq} \quad \forall \tau \quad \text{for} \quad h = 1, \ldots, n_{col} \]  

(3.13)

where \( \bar{c}_{i,h,0} \) and \( \bar{e}_{i,h}^{eq} \) are the concentration of component \( i \) at the inlet and the outlet of the column \( h \), respectively. A different system of ODEs is applicable for each input/output port configuration of the SMB unit. For instance, if the SMB unit includes eight chromatographic columns, one cycle comprises eight switch intervals, with a different set of ordinary differential equations valid in each interval because input/output switching mechanism is explicitly considered by the node balances (see Table 2.1). Each set of ODEs belonging to different configurations can be recast in the following form:

\[ \frac{\partial c}{\partial \tau} = f^p(c, Q) \]  

\[ c_{\text{out}} = g^p(c) \quad \text{for} \quad p = 1, \ldots, n_{col} \]  

(3.14)

where \( Q \) is the vector of the volumetric flow rates in the four sections, i.e., \( Q_1, \ldots, Q_{IV} \), and \( c \) is the vector of the concentration values along the unit, i.e., \( \bar{c}_{i,h,g}(\tau) \) for \( i = A, B, h = 1, \ldots, n_{col} \) and \( g = 1, \ldots, n_g \). \( f^p \) is a vector-valued function

\[ f^p = (f^p_1, \ldots, f^p_{n_{eq}})^T \quad f^p : \mathbb{R}^{(n_{eq}+n_a)} \longrightarrow \mathbb{R}^{n_{eq}} \quad p = 1, \ldots, n_{col} \]  

(3.15)

where \( f^p_1, f^p_2, \ldots, f^p_{n_{eq}} \) are scalar-valued functions. Here \( n_{col} \) denotes the number of different input/output port configurations of the SMB unit. \( g^p \) is another vector-valued function relating the process outputs to the state variables, \( c \);

\[ g^p = (g^p_1, \ldots, g^p_{n_y})^T \quad g^p : \mathbb{R}^{n_{eq}} \longrightarrow \mathbb{R}^{n_y} \quad p = 1, \ldots, n_{col} \]  

(3.16)

where \( g^p_1, g^p_2, \ldots, g^p_{n_y} \) are scalar-valued functions. \( c_{\text{out}} \) are the process outputs, here the concentration levels of two components in the raffinate and extract outlets, i.e., \( \bar{c}_{R}^{eq}(\tau), \bar{c}_{A}^{eq}(\tau), \bar{c}_{B}^{eq}(\tau) \). In the equations above, \( n_y \) and \( n_a \) are the number of process outputs and manipulated variables, respectively, i.e., \( n_y = n_a = 4 \) in this case.
3.1.2 Linearization of the SMB model

The resultant ODE system of SMB (eq 3.14) has some nonlinear terms, i.e., the convective terms in eq 2.10, eq 2.12 and eq 3.7, where concentration and flow rate are multiplied, and they could be linearized at their steady-state values. The SMB process however has no steady-state in which all the process parameters are constant in time. It exhibits a periodic steady-state dynamics in which the process undergoes an identical transient during each period; therefore, the concentration profiles in the SMB unit show a time dependent but period-invariant behavior. Even though the periodicity of the concentration profiles can conceptually be defined over successive switches, in real applications the profiles are periodic only cycle-to-cycle because of the unavoidable variations in single column properties and varying dead volumes between sections. Hence, the linearization of the nonlinear terms can be performed around their cyclic steady-state values. Because the periodic steady-state profile of the SMB is time-varying, the duration of a complete cycle is divided into \( N \) sample points, i.e., \( \tau_s = 0, \ldots, N - 1 \), and the nonlinear model of the system given by eq 3.14 is linearized at each sample point using the corresponding cyclic steady-state concentration values and flow rates in four sections. Note that the reference profile used for linearization at time \( \tau_s \) corresponds to the internal concentration values \( c^{ref}_{i,h,g}(\tau_s) \), where \( i = A, B, h = 1, \ldots, n_\text{col} \) and \( g = 1, \ldots, n_g \). For instance, Figure 3.2 illustrates the reference internal concentration profiles at different time instances, i.e., \( \tau_s = 0, \tau_s = 3 \) and \( \tau_s = 7 \).

The detailed nonlinear dynamic simulation model (described in section 2.2) is used to generate the reference steady-state profiles. Because the whole control concept is based on the idea that the information on the system under consideration is limited, the profiles are generated under the following assumptions.

- The differences between columns due to packing heterogeneity and velocity variations are negligible.

- The SMB unit is operating under linear chromatographic conditions because the linear adsorption isotherm is the only available information about the separation system.

The linearized form of the SMB model takes the following form

\[
\frac{\partial x}{\partial \tau} = J_{f^p}(c)|_{ref} x(\tau) + J_{f^q}(Q)|_{ref} u(\tau) \tag{3.17}
\]

\[
y = J_{g^p}(c)|_{ref} x(\tau) \tag{3.18}
\]

where \( J_{f^p}(c)|_{ref} \), \( J_{f^q}(Q)|_{ref} \) and \( J_{g^p}(c)|_{ref} \) are the Jacobian matrices of the vector-valued functions \( f^p \) (with respect to \( c \) and \( Q \)) and \( g \) (with respect to \( c \)), respectively.
Figure 3.2: Reference concentration profiles of species A and B inside the SMB unit at different sample points, i.e., \( \tau_s = 0, \tau_s = 3 \) and \( \tau_s = 7 \). □ and ○ show the corresponding concentration values of components A and B at grid points defined along the unit, respectively.
All the Jacobian matrices are evaluated at the reference steady-state concentration and flow rate values. $x$, $u$ and $y$ are the state, input and output vectors, respectively, defined in terms of deviation variables. For instance, the state vector comprising the internal concentration values along the unit is defined as $x(t) = c(t) - c_{ref}(t)$. Similarly, the manipulated variable vector is defined as $u(t) = Q(t) - Q_{ref}(t)$. The linearized set of equations can be written in the standard continuous time state-space form.

$$
\dot{x} = A_c(\tau_s) \ x(\tau) + B_c(\tau_s) \ u(\tau) \\
y = C_c(\tau_s) \ x(\tau)
$$

Note that the state-space matrices $A_c$, $B_c$ and $C_c$ are the Jacobian matrices $J_{fp}(c)|_{ref}$, $J_{fp}(Q)|_{ref}$ and $J_g(c)|_{ref}$, respectively. The time argument in the matrices represents the particular time instant at which the linearization is performed. Because the system matrices are changing at each sample point, i.e., $\tau_s = 0, \ldots, N - 1$, one ends up with $N$ different linear model equations constituting the LTV SMB model that describes the dynamics of a complete cycle.

The continuous state-space LTV model equations can be transformed into a discrete time state-space LTV SMB model by using a zero-order hold on the inputs and a sampling time equal to the duration between two successive linearization sample points, i.e., $\Delta \tau_s = n_{col}/N$ (note that the time is dimensionless according to eq 2.1). The continuous time state-space matrices are assumed to be constant over the sampling time $\Delta \tau_s$.

$$
\begin{align*}
x_k(n + 1) &= A(n)x_k(n) + B(n)u_k(n) \\
y_k(n) &= C(n)x_k(n) \quad \text{for} \quad n = 0, \ldots, N - 1
\end{align*}
$$

where, $k$ is the cycle index and $n$ is the time index running within the cycle index. The transition from one cycle to the next one can be written as follows.

$$
x_{k+1}(0) = x_k(N)
$$

This implies that the composition profile at the end of the current cycle $k$ constitute the initial conditions for the next cycle $k + 1$. The resulting LTV state-space model captures both the time dependent cyclic steady-state and the hybrid nature of the process explicitly through the time-varying state-space matrices (eq 3.21) and the cycle-to-cycle transition operator (eq 3.22).
3.1 Modelling

Concentration of component B in extract outlet at steady-state

Concentration of component A in raffinate outlet at steady-state

Figure 3.3: Sampling of the plant outlets. ○, sampling points for the extract outlet; □, sampling points for the raffinate outlet.
There is a critical issue concerning the sampling of the plant outlets. If one inspects the concentration changes at the extract and raffinate outlets between two successive switches, one can see that they attain their highest values at the beginning and end of the switching time at the extract and raffinate outlets, respectively, i.e., they show opposite behavior such that when the concentrations of both components are decreasing in the extract, they are increasing in the raffinate and vice versa (see the concentration profiles of extract and raffinate outlets given in Figure 3.3). Therefore, the output of the model is defined in such a way that the extract outlet is sampled just after the switch, whereas the raffinate outlet is sampled just before the switch (see the sampling points indicated by "○" and "□" in Figure 3.3 for the extract and raffinate outlets, respectively). This method is straightforward to implement because the necessary information is part of the states, i.e., internal concentration profile, and can be extracted easily. From a modelling point of view, this leads to a model in which the dynamics of the most critical period of time for both the extract and raffinate outputs are well taken into account. It also allows for a more accurate calculation of the outlet purities. On the other hand, in practice, the discontinuity due to the port switching cannot result in two different outlet concentration values at the same time. In other words, in reality, one cannot see a difference in concentration levels at the plant outlets just before the switch and just after the switch.

### 3.1.3 Reduction of the model order

The order of the resulting LTV model (eq 3.21 and eq 3.22) is equal to the number of equations constituting the ODE system (3.14) which is determined by the number of grid points defined along each column \( n_g \). For instance, for a binary separation \( n_s = 2 \) and an eight-column SMB unit \( n_{col} = 8 \), defining \( n_g = 10 \) grid points along each column leads to an ODE system comprising 160 equations (see eq 3.10). Thus, the order of the resultant LTV model may lead to a significant computational load for online applications. Fortunately, well established model reduction techniques are available for linear systems and they can be utilized to reduce the order of the model. On the other hand, these techniques are applicable only to time-invariant systems. Therefore, the LTV model is lifted by grouping the input and output values for a complete cycle, i.e., for the time interval \( n = 0 \) to \( N \), to obtain a time-invariant cycle-to-cycle description of the system as given below

\[
x_{k+1}(0) = \Phi x_k(0) + \Gamma U_k \\
Y_k = \Pi x_k(0) + G U_k
\]

where \( N_u \) is the number of inputs and \( N_y \) is the number of plant outputs for the lifted cycle-to-cycle model, i.e., \( N_u = n_u \times N \) and \( N_y = n_y \times N \). In the above equation, \( \Phi, \Gamma, \Pi \) and \( G \) can be interpreted as the state transition, reversed controllability, observability and impulse response coefficient matrices of the system, respectively. Eq 3.23 describes
the transition from cycle $k$ to $k + 1$.

\[ \Phi = A(N - 1)A(N - 2) \cdots A(0) \]  
(3.25)

\[ \Gamma = \begin{bmatrix} (A(N - 1) \cdots A(1)B(0)) & (A(N - 1) \cdots A(2)B(1)) & \cdots & B(N - 1) \end{bmatrix} \]  
(3.26)

\[ \Pi = \begin{bmatrix} C(0) \\ C(1)A(0) \\ \vdots \\ C(N - 1)A(N - 2) \cdots A(0) \end{bmatrix} \]  
(3.27)

\[ \mathbf{G} = \begin{bmatrix} 0 & 0 & \cdots & 0 & 0 \\ C(1)B(0) & 0 & \cdots & 0 & 0 \\ C(2)A(1)B(0) & C(2)B(1) & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ (C(N - 1)A(N - 2) \cdots A(1)B(0)) & \cdots & C(N - 1)B(N - 2) & 0 \end{bmatrix} \]  
(3.28)

\[ \mathbf{Y}_k \] and \[ \mathbf{U}_k \] are vectors grouping the output and input values for one cycle, respectively

\[ \mathbf{Y}_k \triangleq \begin{bmatrix} y_k^T(0) \\ \vdots \\ y_k^T(N - 1) \end{bmatrix}^T, \quad \mathbf{Y} \in \mathbb{R}^{N_y} \]  
(3.29)

\[ \mathbf{U}_k \triangleq \begin{bmatrix} u_k^T(0) \\ \vdots \\ u_k^T(N - 1) \end{bmatrix}^T, \quad \mathbf{U} \in \mathbb{R}^{N_u} \]  
(3.30)

Once the time-invariant cycle-to-cycle model is obtained (eq 3.23 and eq 3.24), the order of the model can be reduced with available model reduction techniques. Here, the balanced model reduction is used [47–49]. Figure 3.4 shows a typical comparison of the reduced-order model output and the nonlinear detailed simulation model output. The order of the model is reduced from 160 to 32 via balanced model reduction.

### 3.1.4 Disturbance modelling

One of the main tasks of the controller is to reduce the effect of disturbances on the process performance. Therefore, prediction of the combined overall effect of all possible disturbances on the plant output is a critical issue affecting the control performance. A description of the disturbance as white noise added to the deterministic models gives poor performance. One possibility is to characterize the disturbances first through available first-principles process models and then incorporate them into the deterministic part of the process model. On the other hand, if the physical sources for disturbances cannot
Figure 3.4: Comparison of reduced-order model output and the nonlinear detailed dynamic simulation model output. $c_A^E$ and $c_B^E$, reduced model output; $c_A^N$ and $c_B^N$, nonlinear detailed dynamic simulation output. $c_A^E$ and $c_B^E$ are the concentrations of species A in the extract and species B in the raffinate, respectively.
be identified, their overall effect on the output can be modelled as a stochastic process. For SMB units two types of disturbances can act on the system. The first type of disturbance is periodwise-persisting, e.g., changes in the feed concentration that are generally experienced for different feed batches, and their effects on the plant output tend to repeat from cycle to cycle. The second type of disturbance is specific to each period, and hence, their effects will be specific to a cycle and will not propagate to the subsequent cycles.

RMPC is based on the idea that, because the possible model prediction errors or the overall effects of periodwise-persisting disturbances on the plant output repeat themselves, they can be modelled directly on the output and compensated by using the information from the previous cycles. The reduced-order lifted model together with the residual term, \( h_k \), which comprises the unknown model error and the influences of the persisting as well as the random disturbances, follows directly from eq 3.23 and eq 3.24

\[
\begin{align*}
\bar{x}_{k+1}(0) &= \Phi \bar{x}_k(0) + \Gamma U_k \\
Y_k &= \Pi \bar{x}_k(0) + G U_k + h_k \\
\bar{x} &\in \mathbb{R}^{\tilde{n}_{eq}}, \quad U \in \mathbb{R}^{N_u}, \quad Y \in \mathbb{R}^{N_y}
\end{align*}
\]

where \( \bar{x} \) is the state vector of the reduced-order lifted model. \( \tilde{n}_{eq} \) denotes the reduced number of states. \( \Phi, \Gamma, \Pi, G \) are the state-space matrices. The term \( h_k \) is modelled with the stochastic difference equation.

\[
\begin{align*}
\bar{h}_{k+1} &= \bar{h}_k + w_k \\
h_k &= \bar{h}_k + v_k
\end{align*}
\]

where, \( h_k \triangleq \begin{bmatrix} h_k^T(0) & \cdots & h_k^T(N-1) \end{bmatrix}^T \quad h \in \mathbb{R}^{N_y}
\]

In the above equation, \( \bar{h}_k \) represents the model prediction error and the effect of periodwise-persisting disturbances that repeat themselves, whereas \( v_k \) can be interpreted as the part that represents the effect of random disturbances. Both \( w_k \) and \( v_k \) are zero-mean white-noise variable sequences with respect to the period index \( k \). It is worth noting that we did not add any noise to the states (see eq 3.31 and 3.32) because we found that this additional degree of freedom does not improve the performance.

### 3.1.5 Unlifting: Time-to-time transition model

The resultant lifted formulation (eq 3.31 and eq 3.32) can be used to develop a period-to-period control algorithm where the future optimal control sequence for a complete cycle is calculated at the beginning of each cycle. An obvious drawback of this approach is its periodwise compensation for the disturbances, which will mostly be effective for the persisting disturbances but not for the instantaneous ones. Therefore, there is a need for a real-time feedback formulation, i.e., a time-to-time transition formulation that utilizes the measurements as they are available, that will overcome this limitation and address the disturbances as they take place.
Notice that the cycle-to-cycle description of the system (eq 3.31 and eq 3.32) can be expressed in terms of incremental changes by differencing the model for two successive cycles as follows.

\[ \Delta \tilde{x}_{k+1}(0) = \hat{\Phi} \Delta \tilde{x}_k(0) + \hat{\Gamma} \Delta U_k \]  
\[ \bar{Y}_k = \bar{Y}_{k-1} + \bar{\Pi} \Delta \tilde{x}_k(0) + G \Delta U_k + \Delta \bar{h}_k, \]  
\[ \bar{Y}_k = \bar{Y}_k + v_k \]

Here, \( \Delta \) indicates the backwards difference with respect to the cycle index, i.e., \( \Delta U_k = U_k - U_{k-1} \) and \( \Delta u_k(n) = u_k(n) - u_{k-1}(n) \). Note that \( \bar{Y}_k \) involves the repeating part of the disturbance effects and \( \bar{Y}_k \) incorporates the effect of random disturbances. Let us define

\[ \delta_k(n) \triangleq \Delta \tilde{x}_{k+1}(0) \quad \text{and} \quad \bar{y}_k(n) \triangleq \bar{Y}_k, \quad \text{with} \quad \Delta u_k(j) = 0 \quad \text{for} \quad j \geq n \quad (3.39) \]

This implies that the same input as for cycle \( k - 1 \) is implemented starting at time \( n \) of the cycle \( k \) and leads to

\[ \delta_k(n) = \hat{\Phi} \Delta \tilde{x}_k(0) + [ \hat{\Gamma}_0 \ldots \hat{\Gamma}_{n-1} ] [ \Delta u_k^T(0) \ldots \Delta u_k^T(n-1) ]^T \quad (3.40) \]

\[ \bar{y}_k(n) = \bar{Y}_{k-1} + \bar{\Pi} \Delta \tilde{x}_k(0) + [ G_0 \ldots G_{n-1} ] [ \Delta u_k^T(0) \ldots \Delta u_k^T(n-1) ]^T + w_{k-1} \quad (3.41) \]

where \( \hat{\Gamma}_n \) and \( G_n \) are the \( n \)th columns of the matrices corresponding to the input at time \( n \), as shown in eq 3.26 and eq 3.28. Note that \( \delta_k(N) = \Delta \tilde{x}_{k+1}(0) \) and \( \bar{y}_k(N) = \bar{Y}_k \) by the definition (eq 3.39). The model equations (eq 3.40 and eq 3.41) can be written for two consecutive time steps, i.e., for time \( n \) and \( n+1 \), and taking the difference, one obtains;

\[
\begin{bmatrix}
\delta_k(n+1) \\
\bar{y}_k(n+1)
\end{bmatrix}
= \begin{bmatrix}
I & 0 \\
0 & I
\end{bmatrix}
\begin{bmatrix}
\delta_k(n) \\
\bar{y}_k(n)
\end{bmatrix}
+ \begin{bmatrix}
\hat{\Gamma}_n \\
G_n
\end{bmatrix}
\Delta u_k(n) \quad (3.42)
\]

\[ y_k(n) = \begin{bmatrix}
0 & H(n)
\end{bmatrix}
\begin{bmatrix}
\delta_k(n) \\
\bar{y}_k(n)
\end{bmatrix}
+ H(n) v_k \quad n = 0, \ldots, N - 1 \quad (3.43)\]

where,

\[ H(n) = \begin{bmatrix}
0 & I & 0 \\
\frac{n_y}{n_y \times n_y} & \frac{n_y}{n_y \times n_y} & \frac{n_y \times (N-1-n_y)}{n_y}
\end{bmatrix} \quad (3.44)\]

Note that the output vector \( y \) comprises the process outputs at time \( n \). The transition
from cycle-to-cycle completes the time-varying description of the system.

\[
\begin{bmatrix}
\delta_{k+1}(0)\\
y_{k+1}(0)\\
z_{k+1}(0)
\end{bmatrix}
= \begin{bmatrix}
\Phi & 0 \\
\Pi & I
\end{bmatrix}
\begin{bmatrix}
\delta_k(N) \\
y_k(N) \\
z_k(N)
\end{bmatrix}
+ \begin{bmatrix}
0 \\
I
\end{bmatrix} w_k
\]

\[ (3.45) \]

The periodic time-varying system of eq 3.42, eq 3.43 and eq 3.45 can be written in the following compact form

\[ z_k(n + 1) = A z_k(n) + B(n) u_k(n) + K_k(n) [y_k(n) - C(n) z_k(n - 1)] \]

\[ y_k(n) = C(n) z_k(n) + H(n) v_k \quad n = 0, \ldots, N - 1 \]

\[ \bar{z}_{k+1}(0) = \bar{y} z_k(N) + \begin{bmatrix} 0 & I \end{bmatrix} w_k \]

which then constitutes the basis for the formulation of the control problem.

### 3.2 Time-varying periodic Kalman filtering

The Kalman filter, which is based on the minimization of the variance of the estimation error, has been accepted as the standard linear optimal state estimator \[44,50\]. A periodically time-varying Kalman filter is found to be best suited for a recursive correction of the model errors by combining the model estimation and the available measurements. The one-step-ahead correction for the time-varying system (eq 3.46 to eq 3.48) are given by

\[ z_k(n + 1|n) = A z_k(n|n - 1) + B(n) u_k(n) + K_k(n) [y_k^{\text{meas}}(n) - C(n) z_k(n|n - 1)] \]

\[ \bar{z}_{k+1}(0|n - 1) = \bar{y} z_k(N|n - 1) \quad n = 0, \ldots, N - 1 \]

\[ (3.49) \]

where \( z_k(n + 1|n) \) denotes the prediction of \( z_k(n + 1) \) based on measurements available up to time \( n \). \( K_k(n) \) is the time-varying Kalman filter gain matrix. Let \( R_v \) and \( R_w \) be the covariance matrices of \( v_k \) and \( w_k \), respectively; then the filter gain is given by

\[ K_k(n) = P_k(n) \bar{C}^T(n) \left[ H(n) R_v H^T(n) + \bar{C}(n) P_k(n) \bar{C}^T(n) \right]^{-1} \]

\[ (3.50) \]

where \( P_k(n) \) is the covariance matrix of the estimate.

\[ P_k(n + 1) = P_k(n) - P_k(n) \bar{C}^T(n) \left[ H(n) R_v H^T(n) + \bar{C}(n) P_k(n) \bar{C}^T(n) \right]^{-1} \bar{C}(n) P_k(n) \]

\[ P_{k+1}(0) = \bar{y} P_k(N) \bar{y}^T + \begin{bmatrix} 0 & I \end{bmatrix} R_w \begin{bmatrix} 0 & I \end{bmatrix} \quad \text{for } n = 0, \ldots, N - 1 \]

\[ (3.51) \]

Instead of using eq 3.50 and eq 3.51 at each time step, one can, once and for all, iterate on the periodically time-varying Riccati difference equation (eq 3.51) until it converges.
to a periodic "steady-state" solution, i.e., \( P_k(n) \rightarrow P_\infty(n) \) with \( n = 0, \ldots, N - 1 \), and obtain the periodic steady-state gain matrices, i.e., \( K_\infty(0), \ldots, K_\infty(N - 1) \), according to the filter gain estimation equation (eq 3.50) [49,51]. Note that because the disturbances are modelled directly on the output (see section 3.1.4), the part of the states denoted by \( \delta \) (see eq 3.39) is not updated. It is passed to the future cycles as a residual information.

### 3.3 Prediction

The \( n_p \)-step-ahead prediction of the plant output based on the measurements up to time \( n \) and the \( n_c \) step future input moves can be obtained from the time-varying process model given by eq 3.46 to eq 3.48.

\[
Y_k^{n_p}(n + 2|n) = S^z(n + 1)\hat{z}_k(n + 1|n) + S^w(n + 1)\Delta U_k^{n_c}(n + 1) \tag{3.52}
\]

for \( n = 0, \ldots, N - 1 \) and \( k = 1, 2, 3, \ldots \)

\( \hat{z}_k(n + 1|n) \) is the state estimate obtained at time \( n \) from the observer (eq 3.49). \( Y_k^{n_p}(n + 2|n) \) and \( \Delta U_k^{n_c}(n + 1) \) consist of the future system outputs and the future input moves, respectively.

\[
\begin{align*}
Y_k^{n_p}(n + 2|n) &= \begin{bmatrix} y_k(n + 2|n) \\ \vdots \\ y_k(n + n_p + 1|n) \end{bmatrix} \\
\Delta U_k^{n_c}(n + 1) &= \begin{bmatrix} \Delta u_k(n + 1) \\ \vdots \\ \Delta u_k(n + n_c) \end{bmatrix}
\end{align*} \tag{3.53}
\]

The matrices \( S^z(n + 1) \) and \( S^w(n + 1) \) are constructed by successive substitution of model equations (eq 3.46 to eq 3.48) for future outputs over \( n_p \) steps as a function of \( n_c \) future input movements. Note that the time index \( n \) is running as a subindex of the cycle index \( k \). For instance, let \( j = n + n_c \); if \( N \leq j < 2N \), then \( j := j - N \) and \( k = k + 1 \). Also note that this interpretation keeps the sizes of the prediction and control horizons fixed.

### 3.4 Optimization of the process performance

The optimization of SMB processes has been addressed by several researchers [31]. On the other hand, regardless of the complexity of the optimization schemes used, the SMB practitioner eventually faces the uncertainties in the system and the challenge of the robust operation of the plant at the calculated optimal operating conditions. Therefore, integration of on-line dynamic optimization and automatic control is required.

For a given plant layout, i.e., total number of columns constituting the SMB unit, their dimensions and distribution in the sections, and a predefined switching time \( t^* \),
the optimization of the SMB process implies the maximization of the productivity, i.e., throughput, and the minimization of the solvent consumption given that the process specifications arising from the hardware limitations, such as maximum allowable pressure drop in the columns or for the pumps, and the product specifications, i.e., the purities of the raffinate and extract outlets, are fulfilled. These specifications can be formulated as constraints in the optimization problem. Note that raffinate and extract purities can be calculated directly from the model outputs (eq 3.46 to eq 3.48) and the corresponding outlet flow rates. Because of the cyclic steady-state nature of SMB units, the concentrations of the species at the plant outlets and so the outlet purities show a periodic time-varying behavior within a cycle; therefore, defining the product specifications on the instantaneous outlet purities would be too stringent. Of main interest is the delivery of products with the given specifications averaged over cycles. Hence, the constraints on the product specifications are defined on the average purities of the extract and raffinate outlets over the prediction horizon, i.e., \( n_p \) cycles.

\[
P^\text{ave}_E(n+1) = \frac{\sum_{i=n+1}^{n+n_p} Q^E_k(i)c^E_{A,k}(i)}{\sum_{i=n+1}^{n+n_p} Q^E_k(i)[c^E_{A,k}(i) + c^E_{B,k}(i)]} \geq P^\text{min}_E \tag{3.54}
\]

\[
P^\text{ave}_R(n+1) = \frac{\sum_{i=n+1}^{n+n_p} Q^R_k(i)c^R_{B,k}(i)}{\sum_{i=n+1}^{n+n_p} Q^R_k(i)[c^R_{A,k}(i) + c^R_{B,k}(i)]} \geq P^\text{min}_R \tag{3.55}
\]

Here, \( Q^E_k \) and \( Q^R_k \) represent the extract and raffinate flow rates, respectively, and can be written in terms of internal flow rates, i.e., \( Q^E = Q_I - Q_{II} \) and \( Q^R = Q_{III} - Q_{IV} \). Because the average purity expressions are nonlinear in the outlet flow rates and concentrations, they are successively linearized at each time step around steady-state values and introduced into the optimization problem as linear inequality constraints. The output concentration profile and flow rate sequence of cycle \( k - 1 \) can be used to linearize the purity equations at cycle \( k \), and moreover, the corresponding values can be updated at each time step by the new outlet measurements and the implemented flow rates. The linearized purity constraints subject to the system by eq 3.52 take the
following form.

\[
P_{E}^{\text{pred}}(n+1) = \mathbf{J}^T_1(n+1)\Delta U^m_1(n+1) + \mathbf{J}^T_2(n+1)\bar{z}_k(n+1|n) + b^E(n+1)
\geq P_{E}^{\text{min}} - s_1 \quad \text{with} \quad s_1 \geq 0
\]

(3.56)

\[
P_{R}^{\text{pred}}(n+1) = \mathbf{J}^T_1(n+1)\Delta U^m_1(n+1) + \mathbf{J}^T_2(n+1)\bar{z}_k(n+1|n) + b^R(n+1)
\geq P_{R}^{\text{min}} - s_2 \quad \text{with} \quad s_2 \geq 0
\]

(3.57)

where \(\mathbf{J}^E_1, \mathbf{J}^E_2, \mathbf{J}^R_1\) and \(\mathbf{J}^R_2\) are gradient vectors and \(b^E, b^R\) are scalars that result from the linearization. If the purity constraints are infeasible, i.e., if there exists no input sequence that satisfies the purity constraints, then this would clearly cause problems for on-line applications. Therefore, the purity constraints are defined as soft constraints by introducing the slack variables \(s_1\) and \(s_2\) that guarantee feasibility for sufficiently large \(s_1\) and \(s_2\) values. The slack variables are included in the cost function and highly penalized to avoid excessive softening of the constraints.

The predicted output concentration values have to be nonnegative to calculate the product purities (given by eq 3.56 and eq 3.57) correctly. Lower bounds on the predicted outputs can be introduced with the following inequality.

\[
y_k^{\text{low}}(n+2|n) \geq y_k^{\text{low}}(n+2) - s_3 \quad \text{and} \quad s_3 \geq 0
\]

(3.58)

where

\[
y_k^{\text{low}}(n+2) = \begin{bmatrix}
y_k^{\text{low}}(n+2) \\
\vdots \\
y_k^{\text{low}}(n+n_p+1)
\end{bmatrix}
\]

(3.59)

is the vector of the output constraint trajectory over the prediction horizon.

Certain constraints on the internal as well as on the external flow rates have to be included not only to be consistent with the physics of the process, but also to ensure a smooth operation of the plant with the available hardware. The implemented constraints on the internal and external flow rates are briefly mentioned here, their detailed description is provided in the Appendix.

- The external flow rates must be nonnegative. Note that constraints on the external flow rates can be easily transformed into constraints on the internal flow rates (refer to Appendix A.1).

- There is a maximum allowable pressure drop in the chromatographic columns. Because sections I and III are subject to the highest flow rates in the unit, their internal flow rates must be limited. Moreover, nonnegativity of the internal flow rates has to be imposed as well (refer to Appendix A.2).
3.4 Optimization of the process performance

- Other constraints on the plant inputs can be defined to ensure a smooth and safe operation. For instance, a maximum allowable rate of change in internal flow rates can be imposed to avoid sudden and significant pressure changes in the columns (refer to Appendix A.3).

- Ideally, SMB units have periodic dynamics over successive switches. Even though modelling of the process periodicity over successive switches would lead to a smaller model with fewer states and inputs, and therefore a smaller problem to be solved on-line, defining the period of the process as a complete cycle allows to correct for periodwise persisting effects of extra-column dead volume differences among the sections and of column-to-column variations. Nevertheless, the controller can be restricted in such a way that the calculated control input sequence has identical values for successive switches. This allows the number of degrees of freedom to be decreased and leads to a smoother operation (refer to Appendix A.4).

The defined inequality constraints on the outputs and the inputs can be combined into the following linear inequality.

$$C_k^{n+1} U_k^{ne}(n+1) \leq C_k(n+1)$$  \hspace{1cm} (3.60)

The defined equality constraints can be grouped in a similar way (refer to Appendix A).

$$C_k^{ne}(n+1) U_k^{ne}(n+1) = C_k^{eq}(n+1)$$  \hspace{1cm} (3.61)

The performance objective for the SMB unit can be defined as maximization of the feed flow rate and minimization of the solvent consumption over the control horizon, i.e., the cumulative solvent consumption and throughput over the control horizon.

$$\min_{\Delta U_k^{ne}(n+1), s_k} \left[ \sum_{i=n+1}^{n+n_e} (\lambda_D(i)Q_D(i) - \lambda_F(i)Q_F(i)) + \lambda_s(n+1)s \right]$$  \hspace{1cm} (3.62)

Here, $\lambda_D$ and $\lambda_F$ are possibly time-varying weights of the desorbent consumption and throughput terms, respectively. $\lambda_s$ comprises the weights of the corresponding slack variables in the cost function, which are chosen to be large relative to the other weights so that the slack variables, i.e., $s$, are kept as small as possible, e.g., $\lambda_D = 4$, $\lambda_F = 20$ and $\lambda_s = 100$. Note that the weights should be chosen by considering the order of magnitude of the corresponding terms in the cost function. The minimization (eq 3.62) together with the linear inequality and equality constraints on the input and output values, given by eq 3.60 and eq 3.61, respectively, constitute a standard linear programming (LP) problem, for which well-established algorithms and commercial solvers are available. On-line solution of the constructed optimization problem provides the optimal flow rate sequence and it is implemented according to a receding horizon strategy; therefore, the element corresponding to the time $n+1$ is implemented on the plant and the remaining
ones are discarded. A new optimization problem is solved at the next time step on the basis of the updated state of the plant. Note that the constraints (eq 3.60 and eq 3.61) and the cost function (eq 3.62) constituting the optimization problem should be considered as a formulation which can be adjusted for specific applications.

ILOG CPLEX 7.0 was used as the commercial LP solver. The maximum computation time to solve the LP, i.e., with approximately 3000 constraints and 280 variables, was found to be 1.2 s on a PC with a 3-GHz processor, which is far below any sampling time that one needs for the on-line optimization based control of the SMB process. The available CPLEX license was server based and one can expect even a shorter calculation time with a local license.

Note that the switch time $t^*$ is not included as a decision variable in the optimization problem because the SMB model used in the control algorithm is developed on the basis of a defined process period, i.e., $n_{col} \times t_{ref}$ (see section 3.1). On the other hand, this does not impose any limitation on choosing a switch time different than $t_{ref}$ for the SMB operation. Because it is only a scaling factor (see section 3.1), one can operate the SMB unit with a different switch time and still use the same controller. Note that the key operating parameters are defined as the flow rate ratios in each section of the SMB unit.

\[ m_j = \frac{Q_j t^* - V \varepsilon}{V (1 - \varepsilon)} \quad (j = I, II, III, IV) \]  

(3.63)

Therefore, the easiest way would be choosing a different switch time for the operation and scale up or down the calculated optimal flow rates according to eq 3.63. Because a lower switch time ($t^*$) means higher internal flow rates ($Q_j$), one needs to pay attention to the pressure drop limitations of the system while doing that.
Implementation of the control concept on a virtual SMB plant

4.1 Control of SMBs under linear chromatographic conditions

This section is dedicated to the implementation of the developed control concept on the virtual SMB plant described in section 2.2. It addresses the on-line optimization based control of SMBs operating under linear chromatographic conditions and assesses the performance and robustness of the control scheme for several scenarios posing the main challenges in SMB operation.

The SMB unit under consideration is a closed-loop four-section eight-column plant arranged in a 2-2-2-2 configuration such as given in Figure 2.2. The chromatographic columns constituting the SMB unit have a length and diameter of 10 and 1 cm, respectively. The process is simulated by neglecting the differences in the single-column properties due to packing differences and velocity variations. The apparent axial dispersion, i.e., $D_{ax,i}$, is defined such that each column has 100 theoretical stages with respect to each solute. The separation system is a binary mixture and its equilibrium behavior is characterized by a linear adsorption isotherm as given below.

$$q_{i,h}^* = H_i c_{i,h} \quad (i = A, B)$$

The Henry's constants characterizing the retention behavior of the two components are $H_A = 4$ and $H_B = 2$, which leads to a selectivity of $S = H_A/H_B = 2$, i.e., a measure of the difficulty for the separation task. Table 4.1 gives the geometrical and physical specifications of the plant as well as the physicochemical properties of the separation system that are used to simulate the process.

The LTV SMB model (eq 3.21 and eq 3.22) that is used in the control scheme is obtained as described in section 3.1. To begin with, the steady-state reference profiles are obtained by simulating the detailed SMB dynamics with the model described in section 2.2 on the basis of system specifications given in Table 4.1 (see Table 4.2 for the reference operating parameters). In this case, the duration of a complete cycle is
Table 4.1: Physical parameters for the nominal SMB plant and the separation system.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of columns</td>
<td>8</td>
</tr>
<tr>
<td>Column distribution</td>
<td>2/2/2/2</td>
</tr>
<tr>
<td>Column diameter, ([\text{cm}])</td>
<td>1</td>
</tr>
<tr>
<td>Column length, ([L, \text{cm}])</td>
<td>10</td>
</tr>
<tr>
<td>Nominal porosity, (\varepsilon_h)</td>
<td>0.7</td>
</tr>
<tr>
<td>Switch time, (t^*), ([\text{s}])</td>
<td>480</td>
</tr>
<tr>
<td>Number of theoretical plates per column, (D_{\text{ap},i})</td>
<td>100</td>
</tr>
<tr>
<td>Henry’s constants</td>
<td>(H_A = 4, H_B = 2)</td>
</tr>
</tbody>
</table>

The control problem is formulated such that the performance of the SMB unit is optimized over 2 cycles and the on-line solution of the optimization problem yields the optimal flow rate sequence for the future 1 cycle, i.e., the prediction and control horizons are defined as \(n_p = 2\) cycles and \(n_c = 1\) cycle, respectively. The economic objective of the operation as well as the desired product purities need to be specified in the cost function (eq 3.62) and constraints (eq 3.56 and eq 3.57) of the optimization problem, respectively. Here, the lowest acceptable purity for the extract and the raffinate is defined as 99\%, i.e., \(P_{E\text{min}} = P_{R\text{min}} = 99\%\), and the delivery of the products with the specified purities constitutes the priority of the operation. The weights of the desorbent consumption and throughput terms in the cost function are chosen as \(\lambda_D = 0.25\) and \(\lambda_F = 1.5\), respectively. The weights of the slack variables are kept relatively large, i.e., \(\lambda_s = 100\), to avoid their excessive use. This mirrors the operating objective such that, once the product specification are fulfilled, the maximization of the throughput has the priority and the cost due to solvent consumption has a secondary importance. Table 4.2 gives the parameters used during the synthesis of the controller.

In all simulations, the plant is operated for one complete cycle at a fixed operating point, namely \(m_I = 4.2, m_{II} = 2.2, m_{III} = 3.8, m_{IV} = 1.9\), and the controller is switched on at the beginning of the second cycle. This is necessary because the control algorithm needs the input and output sequences of the first cycle for initialization. All the simulations include zero-mean white noise added to the output measurements.
### Table 4.2: The parameters used for the controller synthesis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>64</td>
<td>$R_w$</td>
<td>20</td>
</tr>
<tr>
<td>$n_q$</td>
<td>10</td>
<td>$\lambda_D$</td>
<td>0.25</td>
</tr>
<tr>
<td>$m_{ref}^{ref\ldots IV}$</td>
<td>4, 2.1, 3.9, 2.1</td>
<td>$\lambda_F$</td>
<td>1.5</td>
</tr>
<tr>
<td>$n_p$</td>
<td>2 cycles</td>
<td>$\lambda_a$</td>
<td>100</td>
</tr>
<tr>
<td>$n_c$</td>
<td>1 cycle</td>
<td>$P_{E}^{min}$</td>
<td>99%</td>
</tr>
<tr>
<td>$R_v$</td>
<td>1</td>
<td>$P_{R}^{min}$</td>
<td>99%</td>
</tr>
</tbody>
</table>

standard deviation of 2% of the measured concentration value is assumed. The examples below address different types of disturbances that may act on the system and affect the operation performance negatively. The adsorption isotherm parameters, i.e., Henry's constants, are the most significant physical data of the system characterizing the separation of the species. Hence, the operation is highly sensitive to disturbances that cause changes in the isotherm parameters. For some of the examples, the evolution of the product purities for the open-loop operation of the SMB unit, i.e., uncontrolled operation, is also given to illustrate the effects of the disturbances. The open-loop simulations aim only at illustrating the significance of the studied disturbances; therefore, instead of choosing appropriate operating conditions for each case, all open-loop simulations are performed under the same operating conditions, namely those corresponding to the reference operating parameters, i.e., $m_{I}^{ref} = 4$, $m_{II}^{ref} = 2.1$, $m_{III}^{ref} = 3.9$ and $m_{IV}^{ref} = 2.1$.

#### 4.1.1 Case study 1: Step disturbance

The first example shows the performance of the controller when the isotherm parameters undergo a step change, which might occur as the result of sudden temperature changes in the system. With reference to Figure 4.1, the plant is started with the operating parameters given above. Because the columns constituting the SMB unit are initially saturated with the mobile phase only, i.e., there are no solutes, it takes at least a couple of switches for the solutes to reach the outlet positions, i.e., A to reach the extract and B the raffinate. Depending on the operating conditions, it takes more or less time for the impurities, i.e., B in the extract and A in the raffinate, to reach the outlet positions. This behavior can be observed in the purities of the uncontrolled plant. In this particular case, the chosen $m_{II}$ and $m_{III}$ values are correct, whereas $m_{I}$ and $m_{IV}$ lead to poor regeneration in sections I and IV, respectively. As a result, a significant decrease in the extract and raffinate purities starts after three cycles and continues until the unit reaches the cyclic steady-state.

The controller is switched on at cycle 2, and the operating conditions are adapted by the controller such that the purity requirements are fulfilled and the operation per-
Figure 4.1: Outlet purities for the controlled and uncontrolled SMB plant. A step change in the Henry's constants take place at cycle 70, and the constants attain the values $H_A = 4.4$ and $H_B = 2.4$. The minimum required purity is 99% for both outlets.

Performance is optimized. Note that, in the first part of the operation, i.e., until the disturbance takes place, the plant and the model have the same physical parameters, i.e., $H_A = 4$, $H_B = 2$, and the only plant-model mismatch is due to linearization and model reduction.

The disturbance takes place at cycle 70 where the Henry's constants attain the new values $H_A = 4.4$ and $H_B = 2.4$, i.e., corresponding to 10 and 20% changes in $H_A$ and $H_B$, respectively. As a consequence, the selectivity decreases to $S = 1.83$, i.e., 8% less than the nominal value, which implies that the separation task becomes more difficult. The significance of the illustrated disturbance can be observed from the evolution of the product purities for the uncontrolled operation of the plant. Such a disturbance leads to a dramatic reduction in the product purities for the uncontrolled plant (see Figure 4.1). On the other hand, the controller adapts the operating conditions and fulfills the product
4.1 Control of SMBs under linear chromatographic conditions

specification within 5 and 8 cycles for the extract and raffinate outlets, respectively.

In Figure 4.1, note the difference between the set purities, i.e., $P_E^{\text{min}}$ and $P_R^{\text{min}}$ (dotted line in the figure), and the values of the plant outputs under the control action (solid and dashed lines in the figure). The latter are calculated by numerical integration of the continuous plant outputs, thus accurately representing the average purities, i.e., the physically meaningful purities that have to fulfill product specifications. However, these values are not accessible to the controller because the controller is based on information about the plant output sampled only at discrete times. In fact, the average purities used by the optimizer are obtained through the formulas given in eq 3.54 and eq 3.55, hence representing a rather rough approximation of the real values. This is the case even if the predicted and the measured values of the outlet concentrations are the same. The magnitude, as well as the sign, of the differences observed in Figure 4.1 depends on the shape of the composition profiles of the product outputs and decreases as the profiles get smoother. In practice, the output concentration profiles are generally smoother and

Figure 4.2: Controller action in terms of flow rate ratios, i.e., $m_j$ values. The $m_j$ values are calculated by using the average internal flow rates over a cycle.
Implementation of the control concept on a virtual SMB plant

Figure 4.3: Controller action represented in operating parameters spaces, i.e., the \( (m_{II}, m_{III}) \) and \( (m_{IV}, m_{I}) \) operating planes. \( p_1 \) and \( p_3 \) are steady-state operating points for the nominal plant. \( p_2 \) and \( p_4 \) are steady-state operating points after the disturbance. The \( m_j \) values are calculated by using the average internal flow rates over a cycle.

more symmetric because of the unavoidable dead volume in the line from the column outlets to the detectors [43]. Therefore, one might expect that the difference between the specified average purity and the true purity values will be insignificant for practical applications (see section 4.2.5 for a simulated example).

The controller action, in terms of \( m_j \) values, for the whole operation is given in Figure 4.2. Let us interpret the controller action on the \( (m_{II}, m_{III}) \) and \( (m_{IV}, m_{I}) \) planes. With reference to Figure 4.3, the solid lines indicate the complete separation and regeneration regions for the model and for the nominal plant, whereas the areas outlined by dashed lines represent the regions for the actual plant with the new isotherm parameters attained after the disturbance. The points \( p_1 \) and \( p_3 \) indicate the steady-state operating conditions attained during the first part of the operation (nominal plant). It is observed that the controller adapts the operating conditions in such a way that the plant is operated very close to the vertex of the triangular area in the \( (m_{II}, m_{III}) \) plane, i.e., the optimal operating point according to the equilibrium theory, and close to the boundary of the complete regeneration region in the \( (m_{IV}, m_{I}) \) plane.

After the disturbance, the complete separation and regeneration regions for the plant are significantly different. The controller reacts to the changes and drives the operating points into the new separation and regeneration regions in order to fulfill the product specifications as soon as possible. After satisfying the purity requirements, the operating
conditions are adjusted to maximize throughput (the operating point is moved to the vertex of the new complete separation region) and to minimize solvent consumption. The points \( p_2 \) and \( p_4 \) are the new steady-state operating conditions attained after the disturbance.

### 4.1.2 Case study 2: Plant-Model mismatch

Parameter uncertainty concerning the adsorption isotherm of the species to be separated or the column characteristics, i.e., column efficiency, length or porosity, is typically faced in practice. These parameters are difficult to determine and can change during the operation of the unit. The particular example presented here addresses significant uncertainty in isotherm parameters, whereas model bias due to differences in column characteristics is discussed in section 4.2.4. Let us consider a plant with the isotherm parameters \( H_A = 3.35 \) and \( H_B = 2.35 \), i.e., -16 and 17\% different from the corresponding model values, respectively. Note that these Henry's constants lead to a selectivity of \( S = 1.43 \), which implies that the actual separation task is much more difficult than the nominal case. The same startup operating conditions as in the previous example are used for the first cycle. The chosen startup operating parameters correspond to the "no pure outlet" region in the \((m_{II}, m_{III})\) plane (see Figure 2.5) where both the raffinate and extract purities are low.

The evolution of the product purities for the controlled plant is illustrated in Figure 4.4. The controller is able to fulfill the product specifications within eight cycles despite the significant parameter uncertainty. The controller action is given in Figure 4.5 and Figure 4.6. Referring to Figure 4.6, the complete separation and regeneration regions for the model are given by solid lines, whereas the regions indicated by dashed lines correspond to the actual plant. One can see that the complete separation region applicable to the plant is smaller than that corresponding to the model, i.e., the plant is operating with a lower selectivity. On the other hand, the complete regeneration area is such that the separation task requires less-than-nominal fresh solvent. The points indicated as \( p_5 \) and \( p_7 \) show the startup operating points. It can be observed that the controller drives the operating points into the correct separation region as soon as the purities decrease below their required values and then operates the unit close to the vertex of the triangle in the \((m_{II}, m_{III})\) plane. At the same time, it reduces the solvent consumption by adapting the operating conditions in sections I and IV, i.e., the operating point is driven close to the borders of the complete regeneration area in the \((m_{IV}, m_I)\) plane. The points indicated as \( p_8 \) and \( p_8 \) correspond to the steady-state operating points.

The controller action in terms of external flow rates for a complete cycle, comprising eight switches, at steady-state operating conditions is illustrated in Figure 4.7. The inlet flows \((Q^D, Q^F)\) and outlet flows \((Q^E, Q^R)\) are given by dashed and solid lines, respectively. In this case, the time period \( t^* \) between two successive switches is 480 s and is divided into eight segments, constituting 64 sample points for a complete cycle, i.e, \( N = 64 \). It can be seen from Figure 4.7 that the controller is implementing similar
Figure 4.4: Outlet purities for the controlled SMB plant. The isotherm parameters of the actual plant are $H_A = 3.35$ and $H_B = 2.35$, whereas the model parameters are $H_A = 4$ and $H_B = 2$. The minimum required purity is 99% for both outlets.

Figure 4.8 shows the steady-state flow rate sequence implemented between two successive port switches in the $(m_{II}, m_{III})$ and $(m_{IV}, m_I)$ planes. With reference to the $(m_{II}, m_{III})$ operating plane, the first operating point of the switch period is located within the "complete separation" region. Then the controller moves the operating point into the "no pure outlet" region to increase the throughput and drives it back into the complete separation region at the end of the switch period (the direction of the movement is indicated by the arrow). Note that the controller is operating the plant such that the throughput is 19% higher in the second half of the switch period than it is in the first half. It has been recently shown that such operating modes can improve the productivity of SMB units especially with small number of columns [2]. The average operating point corresponds to the steady-state operating point indicated as $p_6$ in Figure
4.1 Control of SMBs under linear chromatographic conditions

Figure 4.5: Controller action in terms of flow rate ratios, i.e., $m_j$ values. The $m_j$ values are calculated by using the average internal flow rates over a cycle.

Figure 4.6: Controller action represented in operating parameters spaces, i.e., the $(m_{II}, m_{III})$ and $(m_{IV}, m_{II})$ planes. $p_5$ and $p_7$ are the startup operating points. $p_6$ and $p_8$ are the steady-state operating points. The $m_j$ values are calculated by using the average internal flow rates over a cycle.
Figure 4.7: Controller action for a complete cycle in terms of external flow rates, i.e., desorbent, extract, feed and raffinate flow rates, at steady-state operating conditions. The period between two successive switches is 480 s, and a complete cycle comprises eight switching periods.

Figure 4.8: Controller action for a switch period in terms of flow rate ratios, i.e., $m_j$ values, at steady-state operating conditions. The moving direction of the operating points are indicated by arrows.
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4.6. One can see that there are six different operating points shown in the figure, that's because two of them are repeated within one switch period. The operating conditions in 
\((m_{1f}, m_f)\) plane are also changing in time. The controller is increasing the amount of fresh desorbent fed into section I during the first half of the switch period and decreasing it during the second half (the direction of the movement is indicated by the arrow). The average operating point corresponding to the steady-state operating point is indicated as \(p_s\) in Figure 4.6.

4.1.3 Case study 3: Gradual changes in the system behavior

Common in SMB operation are slow changes in the characteristics of the system because of chemical and mechanical aging of the solid phase, thus leading to gradual changes in the retention behavior of the species to be separated. This situation can be simulated by implementing a ramp change in the Henry’s constants. Figure 4.9 illustrates a situation in which the isotherm parameters are changing from their initial values, \(H_A = 4\) and \(H_B = 2\), to their final values, \(H_A = 4.4\) and \(H_B = 2.3\), over a time interval of 40 cycles. The first part of the operation corresponds to the nominal case in which the plant and the model have identical isotherm parameters. The change in the Henry’s constants starts at cycle 71 and continues over 40 cycles, i.e., until the end of cycle 110. This results in a continuous decrease in the selectivity, i.e., from \(S = 2\) to \(S = 1.91\). It can be seen that the product purities of the uncontrolled plant exhibit a gradual decrease over the period where the isotherm parameters undergo the ramp change. On the other hand, the controller handles the changes in the system characteristics and fulfills the product specifications throughout the operation.

Figure 4.10 illustrates the gradual shift in the complete separation and regeneration regions because of the changes in the retention behavior of the species. The areas indicated by solid lines correspond to the nominal plant, which is applicable until the isotherm parameters start to change, i.e., until the end of cycle 70. The regions start to shift because of the changes in the Henry’s constants and reach their final position at cycle 110 (depicted by dotted lines). The areas given by dashed lines correspond to the separation and regeneration regions at cycle 95. The controller is adapting the operating conditions to the changes in the characteristics of the system and moves the operating points so as to fulfill the necessary conditions for the high purity separation. The symbols indicate the operating points for the cycle 70, i.e., the steady-state operating conditions for the nominal plant, and for cycles 95, 110 and 130, i.e., the new steady-state operating conditions after the Henry’s constants attain their final values. This example shows the advantage of a real-time feedback formulation that utilizes the measurements as they become available.

Figures 4.1 and 4.9 illustrate two extreme cases, one in which the controller reacts to an instantaneous step disturbance and the products are off-specification during a few cycles and one in which the disturbance is gradual and the controller is able to avoid any off-specification production (Figure 4.9). In Figure 4.11, the transition between
these two types of behavior is investigated. The number of cycles during which either the extract or the raffinate product is off-specification, as a function of the duration of the ramp disturbance (with the overall change of Henry's constants always the same, i.e., $H_A$ from 4 to 4.4, and $H_B$ from 2 to 2.3), is shown. For instance, zero duration corresponds to a step change, and a ramp duration of 40 cycles corresponds to the case reported in Figure 4.9 and Figure 4.10. For a step change in the isotherm parameters, which might occur as a result of sudden temperature changes, the controller can fulfill the product specifications within 6 and 8 cycles for the extract and the raffinate outlets, respectively. If the changes take place over a longer time, the number of off-specification cycles first increases and then decreases, reaching a maximum of about 15 cycles for both extract and raffinate, but at different ramp durations. If the system characteristics undergo a very slow change, which might occur as a result of slow aging of the solid
4.1 Control of SMBs under linear chromatographic conditions

phase, then the controller can adjust the operation so that the product specifications are always fulfilled. The presence of a maximum in the diagrams of Figure 4.11 indicates a competition between two opposite trends. On one hand, increasing the time period over which the same disturbance occurs makes such a disturbance milder and easier to handle by the controller. On the other hand, a sharper disturbance, corresponding to a short ramp duration, yields larger deviations from the required product specifications and activates a faster response from the controller. No special effort has been made to tune the controller. One can optimize the behavior of the controller to obtain that most appropriate for the disturbance dynamics typical of the system under consideration.

Figure 4.10: Trajectory of the operating point and the corresponding complete separation and regeneration regions. o, Steady state operating conditions for the nominal plant; Δ, Operating points at cycle 95; ⋄, operating points at cycle 110; □, Steady-state operating point after Henry constants attain their final values. The \( m_j \) values are calculated by using the average internal flow rates over a cycle.
Figure 4.11: Number of cycles that the plant produces off-specification products versus the duration of the ramp change in the isotherm parameters. The Henry constants $H_A$ and $H_B$ undergo a change of +10 and +15%, respectively, i.e., their final values are $H_A = 4.4$ and $H_B = 2.3$. 
4.2 Control of SMBs under nonlinear chromatographic conditions

This section focuses on the implementation of the control concept to SMBs operating under nonlinear chromatographic conditions. It aims to show that despite the overloaded chromatographic conditions, the process can be controlled and optimized on-line on the basis of only linear adsorption isotherm information. The performance of the control concept is evaluated under different scenarios that are commonly experienced by the SMB practitioners.

The binary system under consideration are the enantiomers of the antitussive agent guaifenesin and its equilibrium behavior is described by the binary competitive Langmuir adsorption isotherm

\[ q^*_i = \frac{H_i c_{iA}}{1 + K_A c_{iA} + K_B c_{iB}} \]  

(4.2)

where \( K_i \) and \( H_i \) are the equilibrium and Henry's constant of the \( i \)th species, respectively. \( A \) and \( B \) indicate the more retained enantiomer, i.e., (S)-(+)guaifenesin, and the less retained enantiomer, i.e., (R)-(−)-guaifenesin, respectively. The isotherm parameters that are used to simulate the process are taken from the available literature [52] and given in Table 4.3. An eight-column four-section closed-loop SMB unit arranged in a 2-2-2-2 configuration is used to separate the racemic mixture. The geometrical and the physical specifications of the plant are provided in Table 4.3. The process is simulated such that the variations in the column properties due to velocity differences are neglected. Unless otherwise stated; the apparent axial dispersion is defined such that each column has 100 theoretical stages with respect to each solute, and the nominal porosity of the columns in the SMB loop is taken as \( \varepsilon_h = 0.7 \). On the other hand, when needed, the differences due to packing heterogeneity are considered by assigning different porosity values for each column. In all simulations, zero-mean white noise with a standard deviation of 2% of the measured concentration value is added to the outlet measurements in order to make the simulations more realistic.

The LTV SMB model (eq 3.21 and eq 3.22) that is used in the control scheme is obtained as described in section section 3.1. Note that even though the separation system is characterized by competitive nonlinear Langmuir isotherm (eq 4.2), the LTV SMB model is developed on the basis of only the linear adsorption information, i.e., the only physical data entering the system of ODEs of SMB (eq 3.14) are Henry's constants \( (H_A = 3.5, H_B = 1.4) \) with eq 3.2 and the average column porosity \( (\varepsilon_{ave} = 0.7) \). The reference cyclic steady-state profiles are generated by simulating the detailed SMB dynamics for an operation under linear chromatographic conditions (see Table 4.4 for the reference operating parameters). The nonlinear ODE system of SMB (eq 3.14) is obtained by defining 40 grid points along each column \((n_g = 40)\) and linearized using the corresponding cyclic steady-state internal concentration and sectional flow rate values.
Table 4.3: Physical parameters for the SMB unit and the separation system.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of columns</td>
<td>8</td>
</tr>
<tr>
<td>Column distribution</td>
<td>2/2/2/2</td>
</tr>
<tr>
<td>Column diameter, [cm]</td>
<td>1</td>
</tr>
<tr>
<td>Column length, L, [cm]</td>
<td>10</td>
</tr>
<tr>
<td>Nominal porosity, εₐ</td>
<td>0.7</td>
</tr>
<tr>
<td>Switch time, t*, [s]</td>
<td>400</td>
</tr>
<tr>
<td>Number of theoretical plates</td>
<td>100</td>
</tr>
<tr>
<td>per column, Dₒₚ,i</td>
<td></td>
</tr>
<tr>
<td>Henry's constants</td>
<td>HA = 3.5, HB = 1.4</td>
</tr>
<tr>
<td>Equilibrium constants</td>
<td>KA = 0.0550, KB = 0.0135</td>
</tr>
</tbody>
</table>

The order of the obtained LTV SMB model was initially 640, i.e., for nₛ = 2, nₙ = 40 and nₑ = 8 according to eq 3.10, nevertheless, it is reduced from 640 to 40 via balanced model reduction as described in section 3.1.3. Table 4.4 gives the parameters used during the synthesis of the controller.

In all cases, the minimum required purities for both outlets are chosen as 99%, i.e., pₑₘᵢₙ = 99%, and the optimization problem is defined such that maintaining the product purities is the primary task for the controller. The weights of the desorbent consumption, feed flow and slack variables in the cost function (eq 3.62) are chosen as λₐ = 4, λₚ = 20 and λₕ = 100, respectively; therefore, once the product specifications are delivered, minimization of the operating cost becomes the primary concern for the control scheme.

In the previous applications, namely the scenarios considered in section 4.1, the controller was allowed to change the flow rates within a switching period, corresponding to so-called PowerFeed operating mode [2,33]. On the other hand, it is also important to devise a strategy to enforce constraints on the way the flow rates are changed, so as to allow for smoother variations if necessary, e.g., all flow rates are constant in traditional SMB operation. Note that the optimization problem, i.e., the constraints (eq 3.60 and eq 3.61) and the cost function (eq 3.62), is a general formulation that can be adjusted for specific applications. On the other hand, because the control problem is formulated as a general optimization problem rather than a tracking or regulation problem and because the cost function is in terms of manipulated variables only, it does not make sense to add penalty terms on the manipulated variables to avoid their excessive use, which is a common practice in MPC formulations to achieve a smooth operation. Here, we demonstrate that the desired smooth operation can be obtained by enforcing identical flow rates over the whole control horizon, i.e., nₑ = 1 cycle, for the internal flows of sections II and III. Also the controller is allowed to change the flow rates in sections I and IV only
4.2 Control of SMBs under nonlinear chromatographic conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>64</td>
<td>$R_v$</td>
<td>1</td>
</tr>
<tr>
<td>$n_g$</td>
<td>40</td>
<td>$R_w$</td>
<td>20</td>
</tr>
<tr>
<td>$H_A$</td>
<td>3.5</td>
<td>$\lambda_D$</td>
<td>4</td>
</tr>
<tr>
<td>$H_B$</td>
<td>1.4</td>
<td>$\lambda_F$</td>
<td>20</td>
</tr>
<tr>
<td>$\varepsilon_{ave}$</td>
<td>0.7</td>
<td>$\lambda_s$</td>
<td>100</td>
</tr>
<tr>
<td>$m^r_{ref}^{I...IV}$</td>
<td>3.57, 1.3, 3.59, 1.37</td>
<td>$P^P_{min}$ = $P^R_{min}$</td>
<td>99%</td>
</tr>
<tr>
<td>$n_p$</td>
<td>2 cycles</td>
<td>$n_c$</td>
<td>1 cycle</td>
</tr>
</tbody>
</table>

Table 4.4: The parameters used for the controller synthesis.

Once at the beginning of each cycle. These flow rates are then kept constant for the rest of the cycle. This was done to demonstrate the possibility of enforcing smoother flow rate changes if desired. Clearly, different alternatives can be proposed to suit specific applications.

Here, several scenarios illustrating the performance of the controller under rather difficult conditions are considered. The control algorithm is initiated by open-loop, i.e., without the controller, operation of the SMB unit for a complete cycle. Because it is assumed that the nonlinear adsorption isotherms are unknown to the SMB operator, it is also assumed that an initial guess of the necessary startup operating conditions based on the isotherm information, e.g., by using the triangle theory, is not possible. Therefore, the plant is simply started-up with the same operating parameters as used for linearization, i.e., $m^r_{ref} = 3.57$, $m^r_{ref} = 1.3$, $m^r_{ref} = 3.59$ and $m^r_{ref} = 1.37$. Because the control concept aims to optimize the economics of the operation, the production cost is given for each scenario in the following. The production cost $F$ is defined similarly to the cost function of the optimization problem (eq 3.62) but the contribution of the slack variables is excluded.

$$ F = \lambda_D Q^D_{ave} - \lambda_F Q^P_{ave} $$

In this equation $\lambda_D$ and $\lambda_F$ are the constants reflecting the prices of the solvent and product, respectively, and they are the same as used in the optimization problem, i.e., $\lambda_D = 4$ and $\lambda_F = 20$. The quantities $Q^D_{ave}$ and $Q^P_{ave}$ are the average values of the solvent and feed flow rates implemented throughout a cycle, respectively.

4.2.1 Case study 1: Operation under overloaded chromatographic conditions

This example illustrates the ability of the controller based on only the linear isotherm information, i.e., the Henry's constants, to find the correct operating conditions for the SMB unit operated under nonlinear competitive adsorption conditions, first to fulfill the
required product specifications and then to optimize the separation performance. In this case, the feed mixture has a total concentration of 9 g/L, i.e., $c_F = 4.5$ g/L and $c_D = 4.5$ g/L. As discussed previously, column-to-column variations are hard to avoid in practice; therefore, it is assumed that the single column porosities of the columns constituting the SMB unit are different, i.e., the average porosity is $\bar{\varepsilon} = 0.7$ and the standard deviation is 2.7%. The assigned porosity values are given in Table 4.5.

The plant is started-up and operated in open-loop mode for a complete cycle with the reference operating conditions, i.e., $m_{rj}^{ref}$, before the controller is activated. The startup operating conditions are within the pure extract region in the $(m_{II}, m_{III})$ plane for the nonlinear separation and far from the corresponding complete separation area. The parameter $m_{rj}^{ref}$ barely fulfills the operating constraint on section I, whereas $m_{IV}^{ref}$ is not low enough to achieve complete regeneration of the liquid phase in section IV, thus leading to pollution of the extract outlet.

Figure 4.12 shows the evolution of the product purities at the controlled plant outlets. The first 100 cycles of the operation comprising the startup phase and the steady-state operation of the SMB unit correspond to the scenario given above; the rest of the operation, i.e., after the disturbance, is discussed in section 4.2.2. It can be seen that the controller can maintain the specified extract purity at all times. On the other hand, it takes 11 cycles to fulfill the required raffinate purity, which is fairly satisfactory considering that the startup operating conditions (indicated as the point $p_1$ in Figure 4.13) are quite far from the conditions necessary for pure raffinate. One can also see that the production cost (F) is minimized and reaches a steady-state value, as do the outlet purities, after 30 cycles. Figure 4.13 illustrates the trajectory of the operating point in the $(m_{II}, m_{III})$ plane under the action of the controller. The corresponding $m_{rj}$ values are calculated with the implemented internal flow rates averaged over one cycle and using the average porosity of the columns. It can be seen that the operating conditions are driven into the complete separation region within 5 cycles and the steady-state operating point indicated by $p_2$ in Figure 4.13 is very close to the vertex of the triangle, which is the optimal operating point in terms of productivity and solvent consumption per unit mass of solid phase according to the triangle theory. The instantaneous external flow rates of desorbent, extract, raffinate, and feed calculated from the implemented internal flow rates are given in Figure 4.14. Note that once the product specifications are fulfilled.
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and the operating conditions are optimized, the flow rates remain constant as in the case of conventional SMB operation.

4.2.2 Case study 2: Step change in the feed concentration

The feed concentration is one of the most important variables characterizing an SMB separation in the case of nonlinear systems. It has a significant impact on the operating conditions to achieve complete separation and regeneration. Triangle theory gives explicit bounds on the operating parameters as a function of feed composition (see section 2.3) that provide a thorough insight into the effects of the feed composition not only on the necessary operating conditions but also on the optimal operating conditions. In practice, SMB separations are designed and optimized with a priori fixed feed concentrations and with the assumption that this feed composition is not subject to change.
Figure 4.13: Controller action represented in \((m_{II}, m_{III})\) operating parameter space. \(m_j\) values are calculated with implemented internal flow rates averaged over a cycle and the average porosity of the columns constituting the SMB unit, i.e., \(\varepsilon_{ave} = 0.7\). \(p_1\), startup operating conditions; \(p_2\), steady-state operating conditions before the disturbance; \(p_3\), steady-state operating conditions after the change in total feed concentration takes place.

On the other hand, differences between different feed batches are a part of practical experience. It is common practice to adapt the operating conditions with the help of available shortcut design tools, e.g., based on triangle theory, to account for the changes in the feed concentration/composition. The effort and time needed to find the necessary operating conditions that fulfill the product specifications depend on the amount and accuracy of the available information on the separation system, i.e., primarily the nonlinear adsorption isotherm, as well as on the experience of the SMB operator. If SMB chromatography is used as part of a continuous process, this approach may not be possible.

This example assesses the performance of the controller when the total feed concentration changes significantly during steady-state operation, i.e., at cycle 100 in Figure 4.12. It is increased by more than 30% from 9 to 12 g/L, i.e., \(c_F^I = 6\) g/L and \(c_F^O = 6\) g/L. The change in the feed concentration necessitates different operating conditions in section II, III and IV. In particular, the complete separation region in the \((m_{II}, m_{III})\)
4.2 Control of SMBs under nonlinear chromatographic conditions

Figure 4.14: Instantaneous external flow rates calculated from the internal flow rates implemented by the controller.

plane becomes smaller and sharper, and accordingly, the unit operation becomes less robust (see the complete separation region with dotted boundaries in Figure 4.13). The vertex of the triangle, i.e., the optimal operating point, shifts downward and to the left, which implies that operating parameters $m_{III}$ and $m_{III}$ have to be decreased in order to maintain the optimal performance. On the other hand, the vertex moves closer to the diagonal, i.e., the difference $(m_{IV} - m_{III})$ decreases, which means that the feed flow rate has to be decreased. The complete separation region reflects the increasing nonlinearity of the SMB dynamics caused by the higher feed concentration. Figure 4.12 shows that the controller can adapt the operating conditions so that the obtained extract purity fulfills the specifications at all times and the required raffinate purity is achieved again within 5 cycles after the $c^F$ change. The process reaches the new steady-state operating conditions after about 10 cycles. The higher feed concentration necessitates lower feed flow rates, i.e., lower $(m_{IV} - m_{III})$ values, and higher solvent consumption to maintain the proper regeneration of the liquid phase in section IV, i.e., lower $m_{IV}$ values according to eq 2.24. As a result, the production cost ($F$) in terms of throughput and solvent consumption increases after the change in the total feed concentration (see
Figure 4.12). Actually, the overall productivity, which is proportional to the product of the total feed concentration and the feed flow rate (eq 2.17), increases by more than 20%. The decreased feed and increased solvent flow rates implemented by the controller are illustrated in Figure 4.14. Note that the new steady-state operating conditions, indicated as the point p3 in Figure 4.13, are very close to the vertex of the new complete separation region, i.e., the optimal operating point for the system with the new total feed concentration 12 g/L.

The disturbance considered here should be regarded as an extreme case. In real plant operation, the changes in feed composition are going to be smaller than the 30% change considered here. It is also possible that the feed composition changes gradually and not suddenly. In all cases, the task of the controller would be easier. This implies that one can expect better performance for the more realistic situations.

### 4.2.3 Case study 3: Gradual changes in the system behavior

Gradual changes in the system characterization are the most common experiences in the SMB operation. Such changes occur, for instance due to mechanical/chemical aging of the stationary phase or a temperature drift, and lead to changes in the retention behavior of the components in the columns. Composition and concentration of the feed batch have a significant effect on the adsorption behavior of the species as it is mirrored by the dependency of the necessary conditions to achieve complete separation and regeneration (see eq 2.22 to eq 2.24). Therefore, in this case study, the total concentration of the mixture to be separated is increased gradually to assess the performance of the controller under such a situation.

The SMB unit is started up with a total feed concentration of 10 g/L, i.e., \( c_F^A = 5 \) g/L and \( c_B^B = 5 \) g/L. Figure 4.15 gives the average outlet purities and the production cost (F) for the whole operation. Following the startup, the product specifications are fulfilled within fewer than 10 cycles. Once the required product purities are reached, the economics of the operation is optimized and the SMB unit is run at steady-state with the minimum production cost (F) after 30 cycles. Figure 4.16 gives the controller action on \((m_{II}, m_{III})\) plane. The complete separation region corresponding to the total feed concentration of 10 g/L is depicted in the same figure by solid lines. It can be seen that the controller first drives the operating point into the correct region in order to fulfill the purity requirements and then optimizes the economics of the operation by moving it to the vertex of the triangle area, i.e., \( \circ \) indicates the steady-state operating point at cycle 60.

Starting from cycle 61, a ramp change in the total feed concentration is implemented to simulate the gradual system behavior change. The total feed concentration reaches to its final value at cycle 120 and becomes 14 g/L, i.e., \( c_F^A = 7 \) g/L and \( c_B^B = 7 \) g/L. The impact of the change in the total feed concentration on the complete separation region can be observed in Figure 4.16. Once the feed concentration starts to increase, the complete separation region starts to shift downwards, becomes smaller and sharper;
Figure 4.15: Average outlet purities and the production cost (F) for the controlled plant. The minimum required purity is 99% for both outlets. The system experiences a gradual change in the total feed concentration, i.e., from 10 g/L to 14 g/L, starting from cycle 61 and ending at cycle 120.

Hence, the operation becomes more nonlinear and less robust. The region of complete separation applied to the plant at cycles 90 and 120, i.e., corresponding to a total feed concentration of 12 and 14 g/L, respectively, is depicted in Figure 4.16. The same figure shows how the controller adapts the operating conditions so that they are always close to the vertex of the shifting complete separation region, e.g., \( \triangledown \) corresponds to the operating point at cycle 90. Thanks to the controller action, the required product purities are maintained throughout the operation despite the 40% gradual increase in the total feed concentration (see Figure 4.15). Note that the production cost (F) is increasing over the period of change (see Figure 4.15). This is necessary because the higher the feed concentration, the closer the vertex of the triangle to the diagonal, i.e., the difference \( (m_{III} - m_{II}) \) becomes smaller as can be seen in Figure 4.16; therefore, the feed flow rate has to be decreased in order to achieve the specified product purities. Once the feed concentration reaches its final value, i.e., 14 g/L, after cycle 120, the
Figure 4.16: Controller action on the \((m_{III}, m_{III})\) operating plane. Different triangles correspond to complete separation regions for different total feed concentration. Model: for linear chromatographic conditions on which the controller is based on. cycle 60: \(c_f^P = 10\) g/L. cycle 90: \(c_f^P = 12\) g/L. cycle 120: \(c_f^P = 14\) g/L. \(\circ\), steady-state operating point corresponding to cycle 60. \(\triangledown\), operating point at cycle 90. \(\Delta\), steady-state operating point after the total feed concentration reaches to its final value, i.e., 14 g/L.

controller operates the unit at the new steady-state operating conditions corresponding to the minimum production operating cost. The final steady-state operating point is indicated by \(\Delta\) in Figure 4.16.

Figure 4.17 gives the internal flow rates in four sections implemented by the controller throughout the operation. One can observe that the controller adapts not only the flow rates in sections II and III, corresponding to the trajectory on \((m_{III}, m_{III})\) operating plane given in Figure 4.16, but it also adapts the flow rates in sections I and IV. The necessary operating condition for the complete regeneration of the liquid phase in section IV is a function of the feed concentration of the less retained compound, i.e., \(c_f^P\). The higher the concentration of the less retained compound in the feed, the lower the necessary flow rate in section IV (see eq 2.24). Therefore, the controller decreases the internal flow rate in section IV to achieve proper regeneration of the liquid phase before it is recycled. On the other hand, the necessary operating condition for the complete
4.2 Control of SMBs under nonlinear chromatographic conditions

regeneration of the solid phase in section I does not depend on the feed concentration (see eq 2.19). Nevertheless, because the violation of the product purities is the most expensive consequence, the controller reacts in all possible ways to guarantee the required purities and increases the flow rate in section I.

It is important to quantify the effect of the considered gradual changes on the separation performance so that the controller performance can be appreciated. Therefore, the same scenario is simulated as follows; the SMB unit is started up with the controller and once it reaches the optimized steady-state operating conditions, i.e., indicated by "o" on (mIII, mIII) plane given in Figure 4.16, the controller is switched off. The rest of the operation is performed with constant operating conditions. Starting from cycle 61, the same ramp change in the total feed concentration is implemented over 60 cycles.

Figure 4.18 gives the average outlet purities for the operation. It can be seen that once the feed concentration starts to increase, i.e., at cycle 61, the raffinate purity starts to decrease significantly and reaches its minimum value of 86.5%. This can be easily explained with the help of the triangle theory. Note that the increase in the feed con-
Figure 4.18: Average outlet purities and the production cost \( (F) \). The minimum required purity is 99% for both outlets. The plant is controlled up to cycle 60, then the controller is switched off and the rest of the operation is performed with constant operating conditions. The gradual change in the total feed concentration is implemented starting from cycle 61, i.e., from 10 g/L to 14 g/L over sixty cycles.

Once the region starts to shift, the constant operating point, i.e., indicated by \( \circ \) in the same figure, falls into the "pure extract region" and leads to low raffinate purity. On the other hand, the extract purity starts to decrease after cycle 110 despite the location of the operating point in the pure extract region. This is not really surprising because the regions defined on the \( (m_{II}, m_{III}) \) operating plane are valid as long as the regeneration of the liquid and solid phases are guaranteed. Note that the concentration of the less retained component increases 20% over 60 cycles, i.e., from 5 to 7 g/L, and the complete regeneration of the liquid phase requires lower flow rates in section IV. Therefore, once the operating condition in section IV becomes insufficient for the regeneration of the liquid phase, the extract outlet is polluted by the recycled liquid and its purity starts to
decrease. The extract purity reaches a final value of 98%.

### 4.2.4 Case study 4: Column variations and efficiency

During the design of an SMB separation, it is common practice to assume that the set of chromatographic columns in the SMB loop have identical packing characteristics, i.e., porosities, although this is hardly probable because of the practical impossibility of packing columns exactly in the same way [53]. Therefore, in practice, the columns constituting the SMB unit have different column packing characteristics that would lead to different retention times of the feed components in each column. One can see from the equation below that the flow rate ratio in each section, i.e., the \( m_j \) value, is a function of the column porosity.

\[
m_j = \frac{Q_j l^* - V \varepsilon}{V(1 - \varepsilon)} \quad (j = I, II, III, IV)
\]

As a result, one might conclude that, because the columns have different porosities, each column in section \( j \) will experience a different \( m_j \) value. According to the results of triangle theory (see section 2.3), complete separation requires that the operating conditions of all columns in section \( j \) fulfill the constraints for that section, e.g., all the columns in section II and III should operate with \( m_j \) values that lie within the triangle complete separation region. It has been shown previously that column-to-column variations can deteriorate the separation performance, especially for SMB units with a small number of columns, and their influence becomes crucial if the columns have low efficiencies. On the other hand, SMB units with more than one column per section are more robust with respect to the changes in the column characteristics [54, 55].

The example presented here analyzes the controller performance for an SMB unit consisting of columns with significantly varying porosities. The porosity values of the single columns have a standard deviation of 7.67%, whereas the overall porosity of the unit, \( \varepsilon_{\text{ave}} \), is 0.7 (see Table 4.6). Moreover, the efficiency of the chromatographic columns is reduced by defining the apparent axial dispersion so that each column has 50 theoretical stages for each solute. The system under consideration has a total feed concentration of 8 g/L, i.e., \( c_F^A = 4 \) g/L and \( c_F^B = 4 \) g/L. Because the SMB under consideration is

<table>
<thead>
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<th>Column, ( h )</th>
<th>( \varepsilon_h )</th>
<th>Column, ( h )</th>
<th>( \varepsilon_h )</th>
</tr>
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<td>0.800</td>
</tr>
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<td>6</td>
<td>0.650</td>
</tr>
<tr>
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<td>0.600</td>
<td>7</td>
<td>0.750</td>
</tr>
<tr>
<td>4</td>
<td>0.805</td>
<td>8</td>
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</tr>
</tbody>
</table>

Table 4.6: Porosity of the columns constituting the SMB unit.
Table 4.7: Column configuration for each port configuration and the corresponding average sectional porosities of each section. The operating parameters, i.e., $m_j$ values, are calculated with the steady-state internal flow rates for each configuration.

<table>
<thead>
<tr>
<th>p</th>
<th>col.</th>
<th>$\varepsilon_I$</th>
<th>$m_I$</th>
<th>col.</th>
<th>$\varepsilon_{II}$</th>
<th>$m_{II}$</th>
<th>col.</th>
<th>$\varepsilon_{III}$</th>
<th>$m_{III}$</th>
<th>col.</th>
<th>$\varepsilon_{IV}$</th>
<th>$m_{IV}$</th>
</tr>
</thead>
<tbody>
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<td>3.334</td>
<td>3-4</td>
<td>0.703</td>
<td>1.180</td>
<td>5-6</td>
<td>0.725</td>
<td>2.931</td>
<td>7-8</td>
<td>0.725</td>
<td>1.308</td>
</tr>
<tr>
<td>2</td>
<td>2-3</td>
<td>0.650</td>
<td>3.350</td>
<td>4-5</td>
<td>0.803</td>
<td>1.272</td>
<td>6-7</td>
<td>0.700</td>
<td>2.770</td>
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<td>0.648</td>
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<tr>
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<td>5-6</td>
<td>0.725</td>
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<tr>
<td>8</td>
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<td>3.334</td>
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<td>0.650</td>
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<td>3.689</td>
<td>6-7</td>
<td>0.700</td>
<td>1.283</td>
</tr>
</tbody>
</table>

Figure 4.19 illustrates the evolution of the product purities for the controlled SMB unit. The controller is activated after open-loop operation of the plant for one complete cycle, as in the previous example. It can be seen that the controller can maintain the purity specification for the extract outlet at all times, whereas the product specification for the raffinate outlet is fulfilled after cycle 17. It is clear that the better the startup operating conditions, the shorter time required for the controller to fulfill the purity requirements. It can also be observed that the economics of the operation is optimized after the product specifications are fulfilled (see the production cost in the same figure) and the steady-state is reached after 40 cycles. The internal flow rates implemented by the controller are illustrated in Figure 4.20. Note that the steady-state flow rates are constant as in conventional SMB operation. On the other hand, the flow rate ratios $m_j$ vary from switch to switch within a cycle because the pairs of columns constituting the sections as well as their porosities are different for each configuration. The $m_j$ value of section $j$ for each configuration calculated with the steady-state internal flow rates are given in Table 4.7.

Figure 4.21 shows the steady-state operating conditions in the $(m_{III}, m_{III})$ plane for each port configuration, i.e., $p = 1, \ldots, 8$. One can see that the average operating point, i.e., the point indicated by the $\square$ in the last figure, is very close to the vertex of the triangle, which represents the optimal operating condition according to triangle theory. The purities of both outlets averaged over one switch period vary because of the varying $m_j$ values (see Figure 4.21), whereas the average purity over the global period, i.e., one cycle consisting of eight switches, is constant (see Figure 4.19). This example shows the
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Figure 4.19: Average output purities for the controlled plant over cycles and the production cost (F). The minimum required purity is 99% for both outlets. The total feed concentration is 8 g/L.

4.2.5 Case study 5: Limitations imposed by the on-line monitoring system

The state-of-the-art measurement systems for the on-line monitoring of absolute enantiomer concentrations are based on the coupling of a UV detector with a polarimeter at each outlet of the SMB unit. The UV detector provides the absorbance of the mixture, which is proportional to the sum of the outlet concentration, i.e., $c_A^R + c_B^E$ and $c_A^E + c_B^R$.的优势在于将过程模型基于全局周期，即一个周期，允许纠正周期内持续的影响，如这里讨论的。注意，由于纯度约束是周期内平均纯度的定义，控制器不受平均纯度变化的影响，只要其平均值在整个周期内满足规格。
Figure 4.20: Instantaneous internal flow rates implemented by the controller

Figure 4.21: Steady-state operating parameters represented in \((m_{III}, m_{III})\) operating parameter space: \(p\), index for port configuration; \(\circ\), operating conditions corresponding to each port configuration; \(\square\), average operating condition.
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Figure 4.22: Concentration profile of component A in the extract outlet: solid line, output profile without dead volume; dashed line, output profile with dead volume. The mixing effect of dead volume is simulated by a well-mixed tank with a volume of 1.5 mL connected to the extract outlet.

whereas the polarimeter provides a signal that is proportional to the concentration difference, i.e., $c_A^R - c_B^R$ and $c_A^E - c_B^E$. The two detectors, i.e., UV and polarimeter, can be calibrated via standard calibration techniques and their signals can be combined to calculate the absolute concentration of each species at the outlets [43].

Recently, detectors for high-pressure applications have been introduced, i.e., UV detectors and polarimeters with high-pressure cells. Even though they can be regarded as robust in a constant pressure environment, available polarimeters show significant sensitivity towards pressure variations, which can occur easily as a result of port switching, column-to-column differences, or flow rate changes during SMB operation. Therefore, it is common practice to locate the detectors at the outlets of the unit, i.e., after the raffinate and extract pumps where the pressure is atmospheric [43]. However, locating the detectors at the low-pressure side after the pumps instead of directly at the col-
Implementation of the control concept on a virtual SMB plant

Figure 4.23: Average output purities for the controlled plant over cycles and the production cost (F). The total feed concentration is 15 g/L, i.e., \( c_F^A = 7.5 \text{ g/L} \) and \( c_F^E = 7.5 \text{ g/L} \). The minimum required purity is 99% for both outlets.

Column outlets have a significant drawback for control applications because the unavoidable dead volume in the line from the internal loop of the SMB to the detectors, i.e., the volume due to the multi-position valves, the piping, and the pumps, introduces mixing effects that have an impact on the outlet concentration profiles. This implies that the measured concentration profiles are smoother than those that would be observed at the withdrawal position in the internal SMB loop and that would correspond to the concentration profiles normally calculated through simulations.

One can model the effect of the dead volume on the output profiles, e.g., by adding a well-stirred tank connected to each outlet of the SMB unit. Figure 4.22 illustrates the concentration profile of the extract outlet for two different cases. The solid lines are the rather sharp profiles calculated with zero dead volume. The dashed lines show the significantly broader profiles obtained by connecting a well-mixed tank with a volume of 1.5 mL to the extract outlet. The areas under the peaks for the two different profiles are the same, as they must be to fulfill the material balances. This implies that the mixing
effect of the dead volume does not change the average purities of the product streams, which are the quantities that matter in evaluating the separation performance.

This example presented here addresses the performance of the controller when the output concentration profiles are affected by the effect of dead volume in the measurement line. The mixing effect caused by the dead volume is simulated by two well-mixed tanks (with a volume of 1.5 mL) connected to the extract and raffinate outlets. The system under consideration has a total feed concentration of 15 g/L, i.e., $c_F = 7.5$ g/L and $c_B = 7.5$ g/L. The same porosity value, i.e., $\varepsilon_h = 0.7$, is assigned to all SMB columns so that the outlet concentration profiles are not affected by column-to-column variations. The startup operating conditions are the same as in the previous examples, i.e., $m_{\text{ref}}$. It can be seen from Figure 4.23 that the controller fulfills the purity requirement for extract and raffinate within 10 and 20 cycles, respectively. Fulfillment of the product specifications is followed by the optimization of the operation economics. The production cost decreases continuously and reaches its minimum at cycle 80. It is observed that the optimization of the economics is relatively slow compared to the cases presented previously. This is due to the combined effect of increased nonlinearity because of the higher total feed concentration and the damped dynamics of the plant outputs. The implemented
internal flow rates are given in Figure 4.24, whereas Figure 4.25 shows the corresponding trajectory of the operating points on the \((m_{II}, m_{III})\) plane. The controller drives the operating point into the correct separation region within 3 cycles, but it takes more time to tune the conditions. The controller moves the operating conditions to the vertex of the triangle within 80 cycles. The steady-state operating point is very close to the vertex of the complete separation area, i.e., the optimal operating point for the system under consideration.

Slight differences can be observed between the specified purities and the attained purities in Figure 4.12, Figure 4.15 and Figure 4.19. This happens because the product purities are calculated on the basis of sampled output profiles (see section 4.1.1 for a detailed discussion). This example shows that when the profiles become smoother because of the mixing effect of the dead volume in the measurement line, which would be the case in real applications, the difference between the specified purity values and the attained purities vanishes (see Figure 4.23).
4.2 Control of SMBs under nonlinear chromatographic conditions

4.2.6 Case study 6: Pump malfunctioning

This section is devoted to show that the on-line optimization based control scheme is capable of not only optimizing the economics of the process but also maintaining the performance of the operation despite the disturbances that might take place due to hardware instabilities. The case study presented here addresses a situation in which the system experiences a pump malfunctioning.

The SMB unit is operated under overloaded chromatographic conditions with a total feed concentration of $10 \text{ g/L}$, i.e., $c_A^f = 5 \text{ g/L}$ and $c_B^f = 5 \text{ g/L}$. The evolution of the average outlet purities and the production cost ($F$) over cycles for the controlled SMB unit are given in Figure 4.26. The first part of the operation, i.e., from startup to cycle 80, corresponds to a smooth operation where the purity requirements are fulfilled, i.e., within less than 10 cycles, and the economics of operation is optimized. The steady-state

![Figure 4.26: Average outlet purities and the production cost ($F$) for the controlled plant. Total feed concentration is $10 \text{ g/L}$. The system experiences a pump malfunctioning, i.e., the feed pump starts to deliver 10% more than it should do at cycle 80.](image-url)
operating conditions with the minimum production cost ($F$) are reached after 30 cycles. Figure 4.27 gives the controller action on the $(m_{II}, m_{III})$ operating space. One can see that the SMB unit is started up with an operating point, i.e., indicated by $p_1$, which is far away from the region of complete separation. Once the controller is switched on, it first drives the operating conditions into the correct region in order to fulfill the required product specifications and then to the vertex of the triangle in order to optimize the economics of the operation. The internal flow rates calculated by the controller and implemented on the plant throughout the operation are given in Figure 4.28. It can be seen that the flow rates in sections I and IV are increased and decreased in order to achieve proper regeneration of the solid and liquid phases, respectively.

The pump malfunctioning takes place at cycle 80, and the feed pump starts to deliver 10% more than it should do. The increase in the feed flow rate affects both the internal flow rates in sections III and IV, i.e., leading to 3 and 4% increase, respectively. This situation has two different effects on the system. First of all, it would lead to a low purity in the raffinate outlet by violating the necessary operating conditions for the separation in section III. The second is that the increase in the internal flow rate of section IV would
lead to improper regeneration of the liquid phase and result in low purity in the extract outlet. It can be observed from Figure 4.26 that the controller rejects the disturbance and recovers the purity of raffinate and extract within 3 and 7 cycles, respectively. There are two main reasons for the longer recovery time of the extract purity compared to the recovery time of the raffinate purity. The first is that it takes at least several switches to see the effect of the disturbance on the extract purity which delays both the reaction of the controller and the effect of the controller action. The second reason is that the controller is allowed to change the flow rates in section I and IV only once a cycle which is imposed to have a smoother operation. Figure 4.28 shows how the controller decreases the flow rates in section III and IV in order to compensate for the increase in the feed flow rate. The controller manages to keep the operating conditions close to the vertex, i.e., the optimal operating conditions for the system under consideration according to triangle theory, despite the disturbances (see the steady-state operating point indicated as \( p_2 \) in Figure 4.27).

![Graphs showing flow rates changes](image)

**Figure 4.28:** Instantaneous internal flow rates implemented by the controller.
Implementation of the control concept on a laboratory SMB plant

This chapter is devoted to the implementation of the control concept on a laboratory SMB plant. The goal is twofold. Firstly, to experimentally evaluate and demonstrate the capability of the controller to operate SMB units under optimal operating conditions in order to exploit the full economic potential in terms of productivity and solvent consumption. Secondly, to show the suitability of the controller even using a minimum of system information, thus making the detailed isotherm measurements redundant and saving time in the separation design phase.

To this aim, the control scheme is implemented on a lab-scale eight-column four-section SMB used for the high purity separation of the nucleosides (uridine and guanosine) retaining on the stationary phase according to a linear isotherm. Several experimental test runs are carried out to challenge the robustness of the controller and to prove its effectiveness.

5.1 Laboratory SMB unit

The laboratory SMB unit consists of eight HPLC columns (10 cm x 1 cm i.d., particle diameter 30 µm) with two columns in each section (2-2-2-2 configuration) and is located in a climate controlled room for isothermal operations (see Figure 5.1). One of the eight modules of the plant setup is shown schematically in Figure 5.2; the module is repeated eight times to constitute the SMB loop shown in Figure 5.3.

Three external streams, i.e., extract (Q_E), feed (Q_F) and raffinate (Q_R), as well as one internal stream, i.e., flow rate of section I (Q_I), are controlled by HPLC pumps (Jasco, PU-987). Five (12+1) port multi-position valves (Vici-Valco EMT-6-CSD12UW), i.e., each associated to one inlet, outlet or solvent recycle line, implement the periodic port switching mechanism (see Figure 5.2). The flow direction is imposed by eight check valves (UPCHURCH, CV-3301), each located between two SMB columns as shown in Figure 5.2. The outlet ports of each column and the inlet ports of the following one are located before and after the check valve, respectively, so that the liquid flow in the unit can be established and cross-contamination can be avoided (see Figure 5.2). The pressure
Figure 5.1: Experimental lab-scale SMB unit.
Figure 5.2: Laboratory SMB setup: repetitive single column building block of the column loop.
after each column as well as the temperature in the unit are monitored. Electronic balances (Mettler Toledo 8700) are used in order to crosscheck the material balance of the system. The operation of the SMB unit is fully automated by using Laboratory Virtual Instrument Engineering Workbench (LabVIEW, National Instruments). The LabVIEW application is designed such that it acts as an autonomous interface to the on-line control scheme [56].

The laboratory SMB setup is arranged in the closed-loop mode, i.e., the fluid phase is withdrawn at the end of section IV and recycled directly to the section I, as illustrated in Figure 5.3. There are different ways to close the loop in an SMB setup. One straightforward method is, as it is adopted in this work, to connect the multi-position valve at the “open loop desorbent outlet” directly to the pump controlling the internal flow rate of section I, i.e., $Q_I$. The recycled stream is connected to a bottle with fresh solvent just before the pump, i.e., with a tee-connection, so that the fresh solvent makes up for the difference in the solvent balance (see Figure 5.2).

Each section of the SMB unit involves extra-column dead volume due to the volume of piping, crossings and check valves. For industrial SMB plants such dead volumes can be neglected because, in general, the ratio between column volume and dead volume is large. However, this is not the case for a lab-scale SMB unit. Figure 5.4 shows the four different dead volume elements that can be identified for each individual SMB column. The physical sources for the dead volume elements can be seen in Figure 5.2. These dead volume elements are measured as $V_{d,a} + V_{d,\beta} = 0.3705$ mL, $V_{d,\gamma} = 0.01$ mL and
Figure 5.4: Dead volume distribution for one column in the experimental SMB setup.

$V_{d,\delta} = 0.041 \text{ mL}$. The dead volume per column in sections I to IV can be calculated from the number of columns and the involved dead volume elements in the corresponding section as follows.

\begin{align*}
V_{d,I} &= \frac{n_{\text{col}}^I(V_{d,\alpha} + V_{d,\beta} + V_{d,\gamma}) + (n_{\text{col}}^I - 1)V_{d,\delta}}{n_{\text{col}}^I} \quad (5.1) \\
V_{d,II} &= \frac{V_{d,\delta} + n_{\text{col}}^{II}(V_{d,\alpha} + V_{d,\beta} + V_{d,\gamma}) + (n_{\text{col}}^{II} - 1)V_{d,\delta}}{n_{\text{col}}^{II}} \quad (5.2) \\
V_{d,III} &= \frac{n_{\text{col}}^{III}(V_{d,\alpha} + V_{d,\beta} + V_{d,\gamma}) + (n_{\text{col}}^{III} - 1)V_{d,\delta}}{n_{\text{col}}^{III}} \quad (5.3) \\
V_{d,IV} &= \frac{n_{\text{col}}^{IV}(V_{d,\delta} + V_{d,\alpha} + V_{d,\beta}) + (n_{\text{col}}^{IV} - 1)V_{d,\gamma}}{n_{\text{col}}^{IV}} \quad (5.4)
\end{align*}

For a 2-2-2-2 column configuration, as in our case, the dead volume per column of each section are calculated to be: $V_{d,I} = V_{d,III} = 0.401 \text{ mL}$, $V_{d,II} = 0.442 \text{ mL}$ and $V_{d,IV} = 0.4165 \text{ mL}$. Note that the way we have implemented the closed-loop configuration introduces a dead volume between the desorbent outlet multi-position valve across the pump to the desorbent inlet multi-position valve (see Figure 5.2). This volume is not part of the column loop, and therefore, it does not influence $V_{d,IV}$. However, in case of incomplete regeneration in section IV, it introduces a short delay time for the profile to propagate from the section IV to the section I.

The following equation allows one to calculate a dead volume correction for the internal flow rates $Q_j$ so that the same constraints on the key operating parameters, i.e., the flow rate ratios $m_j$, (see section 2.3) can be used for the separation design as in the case of a plant without any dead volume [57].

\[ m_j = \frac{Q_j t^* - V\varepsilon - V_{d,j}}{V(1 - \varepsilon)} \quad (j = I, II, III, IV) \quad (5.5) \]
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Note that the control scheme makes use of sectional flow rates as the manipulated variable, thus providing the optimal internal flow rates to be implemented on the plant. These flow rates are imposed on the SMB unit by acting on three external and one internal flow rates, i.e., $Q_E$, $Q_F$, $Q_R$ and $Q_I$. Therefore, the calculated optimal sectional flow rates need to be first corrected for the existing dead volumes according to eq 5.5 and then transformed into the corresponding external flow rates.

\[ Q_{I,\text{pump}} = \left( Q_I + \frac{V_{d,I}}{t^*} \right) \alpha^I \]  

\[ Q_{pump}^E = \left( Q_I - Q_{II} + \frac{V_{d,I} - V_{d,II}}{t^*} \right) \alpha^E \]  

\[ Q_{pump}^F = \left( Q_{II} - Q_{III} + \frac{V_{d,III} - V_{d,II}}{t^*} \right) \alpha^F \]  

\[ Q_{pump}^R = \left( Q_{III} - Q_{IV} + \frac{V_{d,IV} - V_{d,III}}{t^*} \right) \alpha^R \]  

In the above equation, $\alpha^I$, $\alpha^E$, $\alpha^F$ and $\alpha^R$ are the calibration factors of the corresponding pumps that allow to account for their specific pumping behaviors and are determined beforehand. It is worth mentioning that inaccuracies in the pump calibration factors or in the measured sectional dead volumes do not affect the performance of the controller because such a situation has a periodwise-persisting effect on the SMB dynamics which can be corrected by the controller easily (see section 3.1.4).

5.2 Materials and system characterization

In this work, high purity separation of the nucleosides uridine and guanosine (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), on the reversed phase SOURCE30RPC (Amersham Biosciences AB, Uppsala, Sweden) is considered. This stationary phase is designed for fast, high performance preparative separations of bio-molecules such as proteins, peptides and oligonucleotides and has a matrix based on rigid, polystyrene/divinyl benzene 30 µm mono-sized beads. This material is slurry packed into 9 standard stainless steel columns (10 cm × 1 cm) using a solvent mixture of 97% water and 3% ethanol with a flow rate of $Q = 40$ mL/min and 30 min packing time. The ethanol content of the solvent mixture used in the packing procedure is kept low on purpose because operating the SMB unit with a solvent mixture that has a lower ethanol content than the one used for column packing might lead to shrinking of the packing material and might later change the column characteristics.

As the first step of the system characterization, the adsorption behavior of the nucleosides is determined. It is found that they are retained on the stationary phase according to a linear isotherm

\[ q_i = H_i c_i \quad (i = U, G) \]
Figure 5.5: Henry's constants of the nucleosides uridine and guanosine in mixtures of different ratios of ethanol and water at 22°C.

where, U and G denote uridine and guanosine, respectively. The effect of the solvent composition on the adsorption behavior of uridine and guanosine is investigated as illustrated in Figure 5.5. The Henry's constants $H_i$ are calculated from the retention times $t_{R,i}$ of dilute peaks, from which the dead time due to the HPLC dead volume was subtracted first, for ethanol contents from 0% to 10%.

$$H_i = \frac{\varepsilon}{1 - \varepsilon} \left( \frac{t_{R,i} - t_0}{t_0} \right) \quad (i = U, G)$$

In the above expression, $t_{R,i}$ and $t_0$ are the retention time of component $i$ and of non-retained species, respectively. Figure 5.5 shows the Henry's constants of uridine and guanosine in mobile phases with different ethanol/water ratios at 22°C. One can observe that both the selectivity, i.e., $S = H_G/H_U$, and the absolute values of the Henry's constants are increasing with decreasing ethanol content. The SMB operating conditions should be chosen in a way that the selectivity is high, i.e., the region of complete separation is large, so that the separation becomes easier and more robust, and the Henry's constants are small, so that one can use a low switch time $t^*$ and increase the produc-
Table 5.1: Column test with 5% ethanol in water at 22°C; \( c_U = c_G = 0.05 \text{ g/L} \); \( V_{inj} = 20 \mu L \).

<table>
<thead>
<tr>
<th>column nr.</th>
<th>( H_U )</th>
<th>( H_G )</th>
<th>( \varepsilon )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/spare column</td>
<td>1.274</td>
<td>2.168</td>
<td>0.367</td>
</tr>
<tr>
<td>2</td>
<td>1.327</td>
<td>2.293</td>
<td>0.377</td>
</tr>
<tr>
<td>3</td>
<td>1.351</td>
<td>2.334</td>
<td>0.373</td>
</tr>
<tr>
<td>4</td>
<td>1.344</td>
<td>2.324</td>
<td>0.374</td>
</tr>
<tr>
<td>5</td>
<td>1.349</td>
<td>2.328</td>
<td>0.375</td>
</tr>
<tr>
<td>6</td>
<td>1.332</td>
<td>2.301</td>
<td>0.378</td>
</tr>
<tr>
<td>7</td>
<td>1.328</td>
<td>2.295</td>
<td>0.375</td>
</tr>
<tr>
<td>8</td>
<td>1.330</td>
<td>2.268</td>
<td>0.372</td>
</tr>
<tr>
<td>9</td>
<td>1.321</td>
<td>2.248</td>
<td>0.374</td>
</tr>
<tr>
<td>average (2-9)</td>
<td>1.335</td>
<td>2.299</td>
<td>0.375</td>
</tr>
<tr>
<td>( \sigma ) (2-9)</td>
<td>0.011</td>
<td>0.030</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

As a compromise, an ethanol content of 5% is chosen for the experiments and the switch time is fixed at \( t^* = 2 \text{ min} \).

All the columns were tested by injecting a dilute pulse of uridine and guanosine (see Table 5.1). As a result of the tests, columns 2 to 9 are chosen to be used in the SMB loop, whereas column 1, where the shape of the test pulse deviated slightly, is kept as a spare column. The overall void fraction, \( \varepsilon \), of each column is determined by measuring the retention time of a pulse of pure water, which is assumed to be a non-retained species, according to the following equation, where the dead volume of the HPLC was properly accounted for.

\[
t_0 = \frac{V\varepsilon}{Q}
\]

In the equation above, \( t_0 \) is the retention time of the non-retained species, \( V \) is the column volume, and \( Q \) is the volumetric flow rate. Table 5.1 gives the overall void fraction of the columns. Note that the average void fraction \( \varepsilon_{ave} = 0.375 \) is used to design the separation.

The effect of the fluid velocity on the column efficiency (see Van Deemter plot in Figure 5.6) and of the pressure drop (see eq 5.16 in the following) were determined. Column efficiency is expressed in terms of height equivalent to a theoretical plate (HETP)

\[
\text{HETP}_i = a_i + b_i u \quad (i = U, G)
\]

where, the first term on the right hand side accounts for eddy diffusion and the second one accounts for mass transfer resistance [29].

The number of theoretical plates, \( N_{p,i} \), and the HETP can be determined experimentally.
by measuring the peak width at half height ($w_i$) for different fluid velocities under dilute conditions, i.e., for symmetric peaks.

$$N_{p,i} = \frac{L}{\text{HETP}_i} = 5.54 \left( \frac{t_{R,i}}{w_i} \right)^2 \quad (i = U, G) \quad (5.14)$$

According to the lumped solid diffusion model of a chromatographic column under linear conditions, the following relationship applies [35]

$$\text{HETP}_i = \frac{L}{N_{p,i}} = \frac{2\varepsilon D_{Li}}{u_s} + \frac{2u_s}{(1-\varepsilon)H_i a_p k_i} \left( \frac{(1-\varepsilon)H_i}{\varepsilon + (1-\varepsilon)H_i} \right)^2 \quad (i = U, G) \quad (5.15)$$

where $D_{Li} = a_p u_s / 2\varepsilon$. In the above equation, $a_p$ is the specific surface of the adsorbent particles; $u_s$ is the superficial velocity; $k_i$ is the mass transfer coefficient of component $i$. The model parameters for axial dispersion and mass transfer resistance can be estimated by fitting eq 5.15 to the experimental points, and are represented in the caption of

Figure 5.6: HETP measurements (at 22°C) and fitted line according to eq 5.15, where molecular diffusion could be neglected; ($D_{LU} = 0.014$ cm$^2$/s and $D_{LG} = 0.017$ cm$^2$/s at $u_s=1$ cm/s, $a_p k_{LU} = 318.8$ 1/s, $a_p k_{LG} = 253.4$ 1/s).
Figure 5.6, which shows the Van Deemter curves. The pressure drop of the columns is proportional to the velocity and the column length and was measured for an ethanol content of 5% to be:

\[
\frac{\Delta p}{u_d L} = 0.0284 \text{bar min} \left(\frac{\text{cm}^2}{\text{L}}\right)
\]  

(5.16)

## 5.3 On-line monitoring system

The concentration levels in the two outlet streams, i.e., extract and raffinate, are defined as the measured variables and constitute the feedback information for the control scheme (see chapter 3). Because they are non-chiral species, two sensors, i.e., one at each of the outlets, are sufficient to continuously monitor the nucleosides concentration in the binary mixture of the product streams. On the other hand, because the concentrations of the two components can not be measured individually and a superimposed signal is to be expected, two different signals are needed from each sensor. This yields a system of two equations, i.e, one for each signal, with two unknowns, i.e., concentration of the nucleosides, which can be solved for the concentrations \(c_U\) and \(c_G\).

Here, two multi-wavelength UV 2077 detectors (Jasco) are chosen as sensors that provide the required independent signals by measuring the UV absorbance at two different wavelengths simultaneously, thus exploiting the difference in the UV spectra of uridine and guanosine (see Figure 5.7).

Even though simultaneous measurement of UV absorbance at two different wavelengths is sufficient, here we make use of UV signals at four different wavelengths, i.e., \(\lambda_1 = 212\) nm, \(\lambda_2 = 224\) nm, \(\lambda_3 = 244\) nm and \(\lambda_4 = 280\) nm, in order to improve the measurement accuracy and robustness. This leads to the following over-determined system of linear equations that is solved by a least squares regression implemented in the LabView environment

\[
S_{\lambda_n} = k_{\lambda_n}^{U} c_U + k_{\lambda_n}^{G} c_G \quad \lambda_n = \lambda_1, \ldots, \lambda_4
\]

(5.17)

where \(S_{\lambda_n}\) is the UV signal at the wavelength \(\lambda_n\); \(k_{\lambda_n}^{U}\) and \(k_{\lambda_n}^{G}\) are the calibration factors for uridine and guanosine, respectively. The feed concentrations of the SMB experiments are chosen low enough to allow for use of the UVs in the linear range of the calibration curve.

The UV detectors are located between the plant outlet multi-position valve of extract or raffinate and the corresponding pump, as shown in Figure 5.2 and Figure 5.3. At this position, the UVs are at the pressure of the plant. Hence, they are equipped with high pressure flow cells for stable and reliable monitoring. The plant pressure is always below 20 bar, depending on the flow rates. Another option would have been to put the sensors after the outlet pump where the pressure is atmospheric. In this case, the backmixing in the dead volume of the pump and of the tubings would influence the concentration profiles and also introduce a higher time delay. Figure 5.8 shows the
5.3 On-line monitoring system

Figure 5.7: UV spectra of guanosine and uridine measured with a multi-wavelength UV 2077 (Jasco); \( c_U = c_G = 0.08 \text{ g/L} \). For on-line monitoring, signals at the following wavelengths are used: \( \lambda_1 = 212 \text{ nm} \), \( \lambda_2 = 224 \text{ nm} \), \( \lambda_3 = 244 \text{ nm} \), \( \lambda_4 = 280 \text{ nm} \).

Calculated concentrations of uridine and guanosine from the four monitored UV signals during the startup phase of the SMB unit. Figure 5.8-a shows the raffinate outlet concentration profiles for the first 5 cycles, whereas Figure 5.8-b provides a closer view of the concentration profiles in the extract outlet for three switching periods around cycle 5. The dead volume between the multi-position valve at the plant outlet and the detector is almost negligible; therefore, it introduces a time delay of only 3 seconds (at a flow rate of \( Q = 2 \text{ mL/min} \)) for the measured signal. This also implies that there is almost no backmixing in the line between the plant and the detectors and, as can be observed from Figure 5.8, the sensor system monitors the process dynamics very accurately. Note that the pattern of the outlet concentration profiles in Figure 5.8-a makes the small but unavoidable column-to-column variations evident.

The accuracy of the on-line monitoring system is checked by off-line HPLC measurements for a number of SMB experiments and a statistical maximum error of 0.5% on the resulting purity is estimated. This error occurs as the sum of several influences such as calibration deviations at all four UV channels, slight pressure sensitivity of the sensors, drift of the UV signals, and concentration level of the compounds (signal to noise ratio). It has to be kept in mind that the achievable accuracy largely depends on the UV
Figure 5.8: On-line monitoring of the concentrations of guanosine and uridine (5% ethanol in water, $t^* = 2$ min, $m_I = 2.28$, $m_{II} = 1.26$, $m_{III} = 2.29$, $m_{IV} = 1.30$) (a) raffinate (plant startup) and (b) extract (close-up over 3 switch periods).
5.4 SMB separation performance and temperature effects

Characterization of the columns and of the adsorption behavior of the mixture provide us with the information needed for the design of the SMB separation. This section is devoted to the experimental verification of the SMB separation performance before implementing the control scheme. Furthermore the temperature sensitivity of the system is an important issue to be clarified in order to assess the robustness of the SMB experiments. Therefore, the temperature effect on the adsorption behavior of each component, i.e., uridine and guanosine, is characterized by measuring their Henry’s constants at different temperatures (see Figure 5.9-a). Figure 5.9-b illustrates the region of complete separation in the \((m_{II}, m_{III})\) operating plane for different temperatures, and gives an insight into the temperature sensitivity of the separation performance. The operat-

Figure 5.9: (a) Temperature dependence of the Henry’s constants of uridine and guanosine at 5% ethanol in water. (b) the resulting regions of complete separation in the \((m_{II}, m_{III})\) operating plane at different temperatures.

spectra of the two components to be separated and on the possibility of choosing several wavelengths with a significant difference in measurement response. This implies that for a system with a larger difference in spectra, a better accuracy can be achieved. The linearity range of the UV signal at different wavelengths is also a factor to be considered. For the system of guanosine and uridine the spectra are rather close (see Figure 5.7), but a reasonable accuracy can still be obtained.

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Table 5.2: SMB runs at different operating conditions and corresponding purities of raffinate and extract. The flow rate ratios \( m_I \) and \( m_{IV} \) are fixed as 2.89 and 0.88, respectively, and \( t^* = 2 \) min.

<table>
<thead>
<tr>
<th>Run</th>
<th>( m_{II} )</th>
<th>( m_{III} )</th>
<th>( P_R )</th>
<th>( P_E )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.29</td>
<td>1.79</td>
<td>99.8</td>
<td>94.8</td>
</tr>
<tr>
<td>2</td>
<td>1.29</td>
<td>1.79</td>
<td>100.0</td>
<td>95.0</td>
</tr>
<tr>
<td>3</td>
<td>1.32</td>
<td>1.82</td>
<td>99.9</td>
<td>99.1</td>
</tr>
<tr>
<td>4</td>
<td>1.35</td>
<td>1.85</td>
<td>100.0</td>
<td>99.5</td>
</tr>
<tr>
<td>5</td>
<td>1.39</td>
<td>1.89</td>
<td>100.0</td>
<td>99.6</td>
</tr>
<tr>
<td>6</td>
<td>1.41</td>
<td>1.91</td>
<td>100.0</td>
<td>99.6</td>
</tr>
<tr>
<td>7</td>
<td>1.62</td>
<td>2.12</td>
<td>99.6</td>
<td>99.8</td>
</tr>
<tr>
<td>8</td>
<td>1.64</td>
<td>2.14</td>
<td>99.1</td>
<td>99.7</td>
</tr>
<tr>
<td>9</td>
<td>1.68</td>
<td>2.18</td>
<td>95.8</td>
<td>99.8</td>
</tr>
<tr>
<td>10</td>
<td>1.74</td>
<td>2.24</td>
<td>89.7</td>
<td>99.7</td>
</tr>
<tr>
<td>11</td>
<td>1.34</td>
<td>2.07</td>
<td>99.6</td>
<td>99.8</td>
</tr>
<tr>
<td>12</td>
<td>1.31</td>
<td>2.11</td>
<td>99.7</td>
<td>99.3</td>
</tr>
<tr>
<td>13</td>
<td>1.28</td>
<td>2.17</td>
<td>97.4</td>
<td>95.6</td>
</tr>
</tbody>
</table>

Table 5.2: SMB runs at different operating conditions and corresponding purities of raffinate and extract. The flow rate ratios \( m_I \) and \( m_{IV} \) are fixed as 2.89 and 0.88, respectively, and \( t^* = 2 \) min.

The flow rate ratios are fixed as 2.89 and 0.88, respectively, and \( t^* = 2 \) min. The reproducibility of the experiments was tested for one operating point (\( m_{II} = 1.29, m_{III} = 1.79 \)) and a deviation of less than 0.22% in purity was found (see Table 5.2).

The region of complete separation in the \( (m_{II}, m_{III}) \) operating parameter space at 23°C was obtained using the data from single column Henry's constants measurements and is drawn with solid boundaries in Figure 5.10. The validity of this region needs to be verified by SMB experiments. To this aim, SMB experiments with different operating conditions were run to steady-state and the product purities were determined by HPLC measurements. All experiments were carried out at a constant switch time, i.e., \( t^* = 2 \) min, and fixed values of \( m_I \) and \( m_{IV} \), i.e., \( m_I = 2.89 \) and \( m_{IV} = 0.88 \), which guarantee complete regeneration in section I and IV, respectively. The dead volume of the plant was taken into account properly according to eq 5.5 [57]. Table 5.2 reports operating conditions and corresponding purities of raffinate and extract of the experimental runs. First, ten experiments were performed to verify the position of the complete separation region, whereas the last three were performed to identify the optimal operating conditions, i.e., those close to the vertex of the complete separation triangle. The reproducibility of the experiments was tested for one operating point (\( m_{II} = 1.29, m_{III} = 1.79 \)) and a deviation of less than 0.22% in purity was found (see Table 5.2).

Figure 5.10 shows the position of the experimental points on the \( (m_{II}, m_{III}) \) operating plane, whereas the obtained extract and raffinate purities are shown in Figure 5.11. It can be observed that going along the line parallel to the diagonal with increasing \( m_{II} \)-values (see Figure 5.10), the system behaves in the expected way, i.e., the extract purity increases and the raffinate purity decreases (see Figure 5.11-a). On the other hand, it
Figure 5.10: Region of complete separation of guanosine and uridine at 23°C for 5% ethanol in water. Solid line: separation region based on single column Henry’s constants measurements; broken line: separation region estimated from SMB experiments. The operating points of those experiments are indicated, whereas \( t^* = 2 \text{ min} \), \( m_I = 2.89 \) and \( m_{IV} = 0.88 \) were kept constant for all points.

is obvious from Figure 5.10 and Figure 5.11-a that the triangular region of complete separation applied to the SMB unit is slightly shifted with respect to the one obtained using the measured Henry’s constants (given in Figure 5.10 with solid lines). According to the triangle theory, the operating points corresponding to the triangular region lead to 100% purity for both outlets. Here, the maximum achievable purity for both outlets was about 99.6%. Therefore, we have chosen 99% purity as the cutoff criterion and defined the borders of the experimental complete separation region accordingly, this is drawn in Figure 5.10 with dashed boundaries.

Note that the isotherm measurements were performed by controlling the HPLC column temperature, whereas the SMB runs were carried out by controlling the room temperature. Therefore, the mismatch between the complete separation regions determined by isotherm measurements and SMB experiments could be explained by a slightly higher temperature, e.g. ~1°C, inside the columns, whereas the room temperature was stable at about 23°C.

According to the triangle theory, the optimal operating conditions for an SMB separation are at the vertex of the complete separation region. Three more experiments were
run (Run 11 to 13 in Table 5.2) in order to locate the vertex of the triangle region. The position of the operating points in the \((m_{II}, m_{III})\) operating plane is shown in Figure 5.10, whereas Figure 5.11-b gives the corresponding product purities as a function of the corresponding \(m_{III}\)-values.

5.5 Controlled SMB separation of nucleosides

For all experiments given below, the switch time was fixed as \(t^* = 2\) min and the mobile phase was 5% ethanol in water. The operating temperature was chosen as 23°C, but variations in the range of ± 1°C were to be expected due to the limited accuracy of the climate control in the room.

The LTV SMB model (eq 3.21 and eq 3.22) used by the controller is obtained as described in section 3.1 using \(H_U = 1.30\), \(H_C = 2.25\) and \(e_{ave} = 0.375\). These are different from those obtained experimentally by running SMB experiments and used to draw the dashed triangle in Figure 5.10, i.e., \(H_U = 1.316\), \(H_C = 2.140\) and \(e^* = 0.375\). This is done on purpose in order to introduce a plant/model mismatch and to challenge the robustness of the control concept. The initial order of the LTV model was 640, i.e., for \(n_s = 2\), \(n_g = 40\) and \(n_{col} = 8\) according to eq 3.10, nevertheless it is reduced from 640 to 40 via balanced model reduction as described in section 3.1.3. Table 5.3 gives the parameters used for the synthesis of the controller. Note that the number of sampling times within
5.5 Controlled SMB separation of nucleosides

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>64</td>
<td>$R_v$</td>
<td>1</td>
</tr>
<tr>
<td>$n_g$</td>
<td>40</td>
<td>$R_w$</td>
<td>20</td>
</tr>
<tr>
<td>$H_U$</td>
<td>1.30</td>
<td>$H_G$</td>
<td>2.25</td>
</tr>
<tr>
<td>$\epsilon_{ave}$</td>
<td>0.375</td>
<td>$m_{j=I...IV}^{ref}$</td>
<td>2.28, 1.26, 2.29, 1.30</td>
</tr>
<tr>
<td>$n_p$</td>
<td>2 cycles</td>
<td>$n_c$</td>
<td>1 cycle</td>
</tr>
</tbody>
</table>

Table 5.3: The parameters used for the controller synthesis.

A complete cycle is defined to be $N = 64$ and the switching time $t^*$ is 2 min; therefore, the control scheme optimizes the process every 15 s.

5.5.1 Experiment 1: case of plant/model mismatch

Uncertainty in the retention behavior of the species is rather typical in SMB chromatography, e.g., due to measurement errors, temperature deviations, plant dead volume (see section 5.4). Therefore, the SMB control concept should be robust enough to yield good performance under such uncertainties. Hence, we have introduced a plant/model mismatch by developing the controller on the basis of isotherm parameters that are different from the real ones in the SMB plant. This result aims at demonstrating that the controller is able to fulfill the required product specifications and to operate the SMB unit at the optimal operating conditions despite uncertainties in the system behavior that are reflected in errors in the estimation of the model parameters.

The plant was started up without controller at an operating point above the complete separation region ($m_I = 2.28$, $m_{II} = 1.26$, $m_{III} = 2.29$, $m_{IV} = 1.30$), thus leading to purities of $P_P = 90.4\%$ and $P_R = 91.4\%$ at cycle 8 as shown in Figure 5.12. The low product purities are not only due to the wrong choices of the operating point in the $(m_{II}, m_{III})$ plane, but also due to the wrong values of $m_I$ and $m_{IV}$ that lead to improper regeneration in section I and IV. The controller is switched on after cycle 8, to fulfill a specified purity requirement of $P_{mm}^{min} \geq 99\%$ for both extract and raffinate. Recall that the primary task of the controller is the achievement and maintenance of the specified product purities despite uncertainties and disturbances, whereas the secondary task is the optimization of the separation performance in terms of productivity and solvent consumption. This objective is reflected by the cost function of the optimization problem (see section 3.4) where proper weights are chosen, i.e., $\lambda_D = 4$, $\lambda_F = 18$ and $\lambda_s = 100$. Note that the weights are chosen by considering the relative magnitude of each term constituting the cost function rather than their absolute magnitude.

Figure 5.12 shows the purities of extract and raffinate outlets measured by the on-line monitoring system and the production cost ($F$) for the entire operation, i.e., a duration of 54 hours. The production cost ($F$) is defined according to the cost function of the
Figure 5.12: Product purities of extract and raffinate and the production cost \( F \). The controller is switched on after cycle 8 in order to achieve a desired purity of minimum 99% for both products.

The optimization problem (eq 3.62), but without the contribution of the slack variables,

\[
F = \lambda_D Q_D^{ave} - \lambda_F Q_F^{ave} \tag{5.18}
\]

Here, \( Q_D^{ave} \) and \( Q_F^{ave} \) are the average solvent consumption and throughput over a cycle, respectively. One can see from Figure 5.12 that once the controller is switched on, it adapts the operating conditions effectively and fulfills the specified product purities at the expense of the production cost despite the plant/model mismatch. Following the fulfillment of the purity requirements, the production cost is then optimized. Note that if the products purities are above the specifications, there is room for the controller to optimize the economics of the process. The behavior of the controller reflecting this possibility can be clearly observed by looking at the dynamics of the product purities and of the production cost throughout the operation.

Figure 5.13 shows how the controller changed the flow rate ratios in the four sections of the unit during the experiment in order to accomplish the given task. The resulting
trajectory of the operating point with respect to the region of complete separation in the \((m_II, m_{III})\) plane and to the region of complete regeneration in the \((m_{IV}, m_I)\) plane, i.e., defined by \(H_G \leq m_I\) and \(H_U \geq m_{IV}\), are illustrated in Figure 5.14-a and 5.14-b, respectively. The regions with the dashed boundaries correspond to the real behavior in the SMB plant (at 23°C), whereas the regions with the solid boundaries are calculated based on the isotherm parameters used by the controller. One can see that after the controller is activated, i.e., after cycle 8, the operating point in the \((m_{II}, m_{III})\) plane is moved down towards the region of complete separation of the plant (see Figure 5.14-a). Moreover, \(m_I\) and \(m_{IV}\) are changed so as the operating point is moved further inside the region of complete regeneration in order to overcome the regeneration problem (see Figure 5.14-b). Note that the SMB unit is operated close to the vertex of the triangular region (see Figure 5.14-a), which corresponds to the optimal operating conditions according to triangle theory [11].

This result demonstrates that the controller does not need to rely on accurate system
parameters to achieve the product specifications and to optimize the economics of the process.

5.5.2 Experiment 2: case of disturbance in the SMB operation owing to feed pump

As stated above, the task of the controller is to assure the product quality and to operate the SMB unit despite uncertainties and disturbances. Having shown the robustness of the control scheme against uncertainties, here we aim at assessing the performance of the controller when the SMB plant is subject to disturbances. The most common SMB configurations require 4 to 5 pumps and operational problems due to malfunctioning of the pumps are familiar to SMB practitioners. Therefore, in this second test case we considered a situation in which the feed pump starts to deliver 10% more flow from a certain point on and for the rest of the operation.

Before investigating the behavior of the controller under such circumstances, it is important to quantify the effect of such a disturbance on an SMB plant operated without any control scheme, so that the control performance can be appreciated. To this aim, the SMB plant is started up under the same conditions as in the previous case (see

Figure 5.14: (a): Trajectory of the operating point on the \((m_{HI}, m_{HI})\) plane with respect to the region of complete separation. (b): Trajectory of the operating point on the \((m_{IV}, m_{I})\) plane with respect to the region of complete regeneration. The regions given by dotted line are valid for the SMB plant, whereas the ones with solid line are based on the isotherm information used to obtain the SMB model of the control scheme.
section 5.5.1) and run until it reaches steady-state. The feed flow rate is increased by 10% after cycle 47 in order to illustrate the effect of such a disturbance on the separation performance of an uncontrolled SMB unit. Figure 5.15 gives the corresponding plant response in terms of product purities. It can be seen that the start up operating conditions lead to a purity of about 94 and 92% for extract and raffinate, respectively, whereas the change in the feed flow rate results in a 7% decrease in the purity of both outlets. It is worth pointing out that the extract and raffinate purities are fluctuating slightly even at steady-state conditions. This is probably due to temperature variations in the system and possibly also due to pulsations of the pumps. This actually indicates that the system is already subject to disturbances that are hard to avoid completely.

The controlled SMB operation is started up under the same initial conditions as in the case illustrated in Figure 5.15 and the controller is switched on after the first cycle. The
Implementation of the control concept on a laboratory SMB plant

Figure 5.16: Product purities of extract and raffinate and production cost (F). The controller is switched on after cycle 1 in order to achieve a desired purity of above 98.5% for both products. The disturbance on the feed pump (unknown to the controller) is implemented at the end of cycle 100 by changing the pump calibration factor and the feed pump starts to deliver 10% more than it should do.

The specified minimum purity requirement is defined as $P_{min} \geq 98.5\%$ for both extract and raffinate. This constraint is fulfilled after about 25 cycles following the start up (see Figure 5.16). The disturbance, which is of course unknown to the controller, is implemented after cycle 100. The feed pump delivers 10% more flow for the rest of the operation. This is done by changing the calibration factor of the feed pump (see eq 5.8). It can be observed from Figure 5.16 that the controller rejects the disturbance and recovers the required outlet purities within 20 cycles at the expense of the production cost. Once the product specifications are achieved, the cost is improved and then optimized.

Figure 5.17 illustrates the controller action in terms of flow rate ratios, $m_j$, throughout the operation. The implemented disturbance affects directly the flow rates in sections III and IV by increasing them. One can see that the controller counteracts and compensates
Figure 5.17: Controller action throughout the operation in terms of flow rate ratios \(m_\text{i,j}\) that are calculated by average internal flow rates over one cycle. The disturbance on the feed pump (unknown to the controller) is implemented at the end of cycle 100 and feed pump starts to deliver 10% more than it should do, which causes the discontinuity in \(m_{\text{III}}\) and \(m_{\text{IV}}\).

for the consequences of the increased feed flow rate. The controller operates the plant very close to the vertex of the complete separation region in the \((m_{\text{II}}, m_{\text{III}})\) plane both before and after the disturbance.

As a final remark, this operation is carried out by using slightly different weights in the cost function of the optimization problem with respect to the test case in section 5.5.1, i.e., \(\lambda_D = 2\), \(\lambda_F = 4\) and \(\lambda_s = 100\). It is observed that the values of the weights do not have a significant influence on the controller performance provided that there is a clear difference in the relative magnitude of the terms constituting the cost function, i.e., \(\lambda_D Q_D^n\) and \(\lambda_F Q_F^n\) in eq 3.62.
5.5.3 Experiment 3: case of disturbance in the SMB operation owing to recycle pump

The third and the last experimental test addresses a similar case to the one considered in section 5.5.2, but this time the disturbance takes place because of the recycle pump and it poses a more challenging situation for the controller.

The SMB unit is started up without controller under inappropriate operating conditions, i.e., \( m_I = 2.28, m_{II} = 1.26, m_{III} = 2.29, m_{IV} = 1.30 \), thus leading to low product purities (see Figure 5.15 for an uncontrolled operation under the same operating conditions). Figure 5.18 shows the product purities and the production cost (eq 5.18) for the entire operation, i.e., 38 hours. Note that the extract purity starts from 90% at
the startup, this is because the SMB columns were not free of nucleosides initially. The controller is switched on after cycle 8 to fulfill a specified purity of $P^{\text{min}} \geq 99\%$ for both.

The disturbance is implemented after cycle 49 such that the recycle pump starts to deliver 5% more for the rest of the operation. Note that the SMB plant is designed such that the internal flow rate of section I is controlled directly by the recycle pump. The recycle line has a tee-connection to a fresh solvent container so that the fresh solvent makes up for the difference in the solvent balance (see section 5.1). This means that the implemented disturbance on the recycle pump directly affects all sectional flow rates by increasing them. A 5% percent increase in the flow rate of section I leads to approximately 8, 5 and 9% increase in the flow rate of section II, III and IV, respectively (see Figure 5.20).
Figure 5.20: Controller action throughout the operation in terms of flow rate ratios \(m_j\) that are calculated by average internal flow rates over one cycle. The disturbance on the recycle pump (unknown to the controller) is implemented at the end of cycle 49 and recycle pump starts to deliver 5% more than it should do, thus causing a sudden increase in all \(m_j\) values.

Figure 5.19-a illustrates the effect of the disturbance on the \((m_{II}, m_{III})\) operating plane. The operating conditions just before and just after the disturbance are indicated as \(p_2\) and \(p_3\), respectively. One can see that the sudden increase in the sectional flow rates moves the operating point to the "pure extract" region and leads to a fast decrease in the raffinate purity. Nevertheless, the controller rejects the disturbance and recovers the product purity within 20 cycles as shown in Figure 5.18. Figure 5.19-b illustrates the controller action on the \((m_{II}, m_{III})\) operating plane starting from the time that the disturbance takes place to the end of the operation. One can see that the controller drives the operating point first towards the complete separation region in order to fulfill the purity requirements as soon as possible. Once the purity specifications are achieved, the economics of the operation is optimized by moving the operating point to the vertex
of the triangular area. It is noteworthy to mention that variations in the room temperature were a part of the practice especially concerning the day and night operations. Therefore, deviations in the location of the complete separation region given in Figure 5.19, which is valid at 23°C, is to be expected (refer to Figure 5.9 for the temperature sensitivity of the separation). As a final remark, one can see that the controller provides a smoother operation compared to the previous experimental runs (see section 5.5.1 and section 5.5.2). Previously, the measurement delay due to the dead volume between the plant outlets and the sensors were considered but we realized that the UV sensors also have a response delay. Hence, this improvement is obtained by accounting for the total delay time properly and by sampling the product outlets such that the concentration peaks are captured at the right time instances. Please refer to section 3.1.2 for a detailed discussion on the importance of the sampling strategy.

The results given here and in section 5.5.2 demonstrate that the controller can minimize the off-spec production, assure the product quality and optimize the performance of the plant despite major disturbances in the SMB operation.
Conclusions and Outlook

Simulated moving bed chromatography has become a widely used separation technology for complex separation tasks that are regularly encountered in the areas of pharmaceutical, fine chemicals and biotechnology. However, operation of SMBs at their economic optimum was still an open issue because of the absence of proper process control schemes. The previously proposed SMB control concepts were highly depended on the availability of accurate physicochemical data and the precise representation of the process dynamics.

In this thesis, the SMB control problem is addressed as a general constrained dynamic optimization problem. The developed SMB control scheme has several noteworthy features. First of all, it requires minimal information on the adsorption behavior of the separation mixture as well as on the columns in the SMB loop. The required physical parameters, namely Henry's constants and average column porosity, need to be determined off-line once and for all. Therefore, it is the only SMB controller that makes the detailed characterization of the system redundant. Moreover, it is the only control scheme that can handle column-to-column and section-to-section differences thanks to its cycle-to-cycle formulation.

The effectiveness of the controller has been demonstrated when applied to a virtual SMB plant in the case of systems characterized by both linear and nonlinear isotherms. The performance has been tested thoroughly under extreme model/plant mismatch conditions and disturbances of various origins.

It has been also shown that the controller works indeed also on an experimental SMB plant, which in this case is a 8-column SMB unit used for the separation of the nucleosides, namely uridine and guanosine. Several experimental runs have been carried out to challenge the robustness of the controller and it has been verified that the controller does not need to rely on accurate system parameters to assure the product quality and to optimize the economics of the process despite major disturbances in the SMB operation. No special effort has been made to tune the controller to get a better performance. Choosing the weight factors in the cost function (eq 3.62) along the lines of the economic objective of the operation was found to be sufficient.

These results open up rather promising perspectives in SMB chromatography because the control scheme provides the possibility of starting a preparative SMB separation on the basis of minimum information, thus reducing the process development time significantly. Moreover, it also delivers the maximum productivity at minimum cost. This
looks particularly attractive for chiral systems and for multicomponent separations where adsorption characterization may be very time consuming.

The introduced concept is applicable to different operating modes of SMBs, e.g., PowerFeed, ModiCon and VARICOL (for predefined switching intervals), as well as to reactive SMB processes. On the other hand, its experimental implementation for a system characterized by a nonlinear adsorption isotherm, i.e., preferably a chiral system, needs to be considered with high priority because such systems are of significant interest in industry.
Formulation of constraints

A.1 Constraints on the external flow rates

Nonnegativity of external flow rates ($Q^E$, $Q^R$, $Q^F$) can be imposed through internal flow rates.

\begin{align*}
Q^E &= Q_I - Q_{II} \geq 0 \\
Q^R &= Q_{III} - Q_{IV} \geq 0 \\
Q^F &= Q_{III} - Q_{II} \geq 0
\end{align*}

Let $V$ be the $(m \cdot n_c) \times (n \cdot n_c)$ block diagonal matrix of the form

\begin{equation}
V = \begin{bmatrix}
v & 0 & \cdots & 0 \\
0 & v & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & v
\end{bmatrix}
\end{equation}

where $m$ and $n$ is the number of rows and columns of the matrix $V$, respectively. $n_c$ is the length of the control horizon and the matrix $v$ is defined as

\begin{equation}
v = \begin{bmatrix}
1 & -1 & 0 & 0 \\
0 & 0 & 1 & -1 \\
0 & -1 & 1 & 0
\end{bmatrix}
\end{equation}

The nonnegativity of feed, extract and raffinate flow rates for the whole control horizon can be enforced by

\begin{equation}
V \Delta U^{ex}_k(n+1) \geq -V(Q^{ref}_k + U^{ex}_{k-1}(n+1))
\end{equation}

$Q^{ref}_{k}$ is a vector consisting of the reference internal flow rates grouped for the whole control horizon. $U^{ex}_{k-1}(n+1)$ is the input sequence of the previous cycle defined in the same way as $U^{ex}_k(n+1)$ given by eq (3.53).
A.2 Lower and upper bounds on the internal flow rates

Lower and upper bounds for the control inputs, i.e. on the internal flow rates, can be defined with the following inequalities:

\[- \Delta U^\text{ne}_k(n+1) \geq -U^\text{ne}_\text{max} + U^\text{ne}_{k-1}(n+1)\]  \hspace{1cm} (A.7)
\[\Delta U^\text{ne}_k(n+1) \geq U^\text{ne}_\text{min} - U^\text{ne}_{k-1}(n+1)\]  \hspace{1cm} (A.8)

where upper and lower bounds are defined in terms of deviation variables:

\[U^\text{ne}_\text{max} = Q^\text{ne}_\text{max} - Q^\text{ne}_{\text{ref}}\]  \hspace{1cm} (A.9)
\[U^\text{ne}_\text{min} = Q^\text{ne}_\text{min} - Q^\text{ne}_{\text{ref}}\]  \hspace{1cm} (A.10)

\[Q^\text{ne}_\text{max}\] and \[Q^\text{ne}_\text{min}\] are the vectors consisting of the maximum and minimum allowable internal flow rates grouped for the whole control horizon, respectively.

A.3 Constraints on the maximum internal flow rate changes

Let \(\delta\) indicate the difference with respect to the time index, i.e. \(\delta Q_k(n+1) = Q_k(n+1) - Q_k(n)\). The rate of input change can be bounded as

\[|\delta Q_k(n+1)| \leq \delta Q^\text{max}\]  \hspace{1cm} (A.11)

Implementation for the whole control horizon follows

\[-J_3 \Delta U^\text{ne}_k(n+1) \geq -\delta Q^\text{ne}_\text{max} + J_3 U^\text{ne}_{k-1}(n+1) - J_4 u_k(n)\]  \hspace{1cm} (A.12)
\[J_3 \Delta U^\text{ne}_k(n+1) \geq -\delta Q^\text{ne}_\text{max} - J_3 U^\text{ne}_{k-1}(n+1) + J_4 u_k(n)\]  \hspace{1cm} (A.13)

where,

\[J_3 = \begin{bmatrix} I & 0 & \cdots & 0 & 0 \\ -I & I & \cdots & 0 & 0 \\ 0 & -I & \cdots & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & -I & I \end{bmatrix}\]  \hspace{1cm} and \hspace{1cm} \[J_4 = \begin{bmatrix} I \\ 0 \\ \vdots \\ 0 \end{bmatrix}\]  \hspace{1cm} (A.14)

\(\delta Q^\text{ne}_\text{max}\) is the vector consisting of the maximum allowable flow rate change for the whole control horizon and \(u_k(n)\) is the control input implemented at time \(n\).
A.4 Identical control input sequence for successive switches

Identical control inputs for successive switches can be implemented in different ways, one of which is given below.

\[ J_5 \Delta U_k^{nc} (n+1) = -J_5 U_k^{nc} (n+1) \]  \hspace{1cm} (A.15)

where,

\[
J_5 = \begin{bmatrix}
I^s & -I^s & 0 & \cdots & 0 \\
I^s & 0 & -I^s & \cdots & 0 \\
\vdots & \vdots & \ddots & \ddots & \vdots \\
I^s & 0 & \cdots & 0 & -I^s
\end{bmatrix}
\hspace{1cm} (A.16)
\]

Note that the identity matrix denoted by \( I^s \) has a dimension of \((n_u \cdot N_{tot}) \times (n_u \cdot N_{tot})\) where \( N_{tot} \) is the number of sampling times between two successive switches.

A.5 Grouping inequality and equality constraints

The defined inequality constraints can be put into

\[ C_k^u(n+1) \Delta U_k^{nc} (n+1) \geq C_k(n+1) \]  \hspace{1cm} (A.17)

where,

\[
C_k^u(n+1) = \begin{bmatrix}
I \\
-I \\
V \\
-J_3 \\
J_3 \\
S^u(n+1) \\
J^P_k(n+1) \\
J^P_k(n+1)
\end{bmatrix}
\hspace{1cm} (A.18)\]
and

\[ C_k(n+1) = \begin{bmatrix}
U_{\text{min}} - U_{k-1}^n(n+1) \\
\delta U_{\text{max}} - \Delta U_{k-1}^n(n+1) \\
-\delta Q_{\text{max}}^n + J_3 U_{k-1}^n(n+1) - J_4 u_k(n) \\
-\delta Q_{\text{max}}^n - J_3 U_{k-1}^n(n+1) + J_4 u_k(n) \\
\gamma_k^\text{low}(n+2) - S^k(n+1) z_k(n+1|n) - s_3 \\
P_{\text{max}}^n - J_5^k(n+1) z_k(n+1|n) - b_{\text{max}}(n+1) - s_1 \\
P_{\text{min}}^n - J_5^k(n+1) z_k(n+1|n) - b_{\text{min}}(n+1) - s_2
\end{bmatrix} \] (A.19)

The defined equality constraints can be written as

\[ C_k^{\text{eq}}(n+1) \Delta U_k^n(n+1) = C_k^{\text{eq}}(n+1) \] (A.20)

where

\[ C_k^{\text{eq}}(n+1) = J_5 \quad \text{and} \quad C_k^{\text{eq}}(n+1) = -J_5 U_{k-1}^n(n+1) \] (A.21)
Patents


Journal articles


Conference articles


Technical Reports

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